THE QUARTERLY JOURNAL OF MEDICINE

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NEW SERIES, VOLUME XIII
(VOLUME XXXVII OF THE CONTINUOUS SERIES)
1944

OXFORD
AT THE CLARENDON PRESS

OXFORD UNIVERSITY PRESS
AMEN HOUSE, E.C. 4
LONDON EDINBURGH GLASGOW NEW YORK
TORONTO MELBOURNE CAPETOWN BOMBAY
CALCUTTA MADRAS
HUMPHREY MILFORD
PUBLISHER TO THE UNIVERSITY

PRINTED IN GREAT BRITAIN AT THE UNIVERSITY PRESS, OXFORD
BY JOHN JOHNSON, PRINTER TO THE UNIVERSITY

CONTENTS

NEW SERIES, VOLUME XIII, NUMBER 49, JANUARY 1944

NUMBERS 50, 51, APRIL–JULY 1944

NUMBER 52, OCTOBER 1944

INDEX OF CONTRIBUTORS

616.74–009

MYASTHENIA GRAVIS: A CONSIDERATION OF ITS CAUSATION IN A STUDY OF FOURTEEN CASES[1]

By ANDREW WILSON and H. BERRINGTON STONER
(From the Department of Pharmacology and Therapeutics, University of Sheffield, and the Royal Sheffield Infirmary and Hospital)

With Plate 1

The modern conception of the mechanism at fault in myasthenia gravis centres round certain possible physiological disturbances.

I. That the cholinesterase activity at the myoneural junction is abnormal and does not permit the normal action of acetylcholine.

II. That the amount of acetylcholine liberated at the myoneural junction is less than normal.

III. That some by-product of acetylcholine prevents the normal action of acetylcholine, or that some 'curare-like' substance blocks the receptor mechanism with a similar effect.

These possibilities have been investigated in a series of cases of myasthenia gravis.

Cholinesterase Activity

Owing to the difficulties involved in obtaining specimens of human muscle for comparative determinations of cholinesterase activity, most investigators of myasthenia gravis have made use of serum. Indeed, a résumé of the literature shows that in only two cases of myasthenia gravis has a specimen of muscle been examined (Jones and Stadie, 1939; Goodman, Carlson, and Gilman, 1939). These workers did not find any material increase in the cholinesterase activity of myasthenic muscle as compared with normal muscle. Three main methods are described for the estimation of serum cholinesterase activity, manometric, volumetric, and biological.

Stedman (1935), using a Barcroft differential manometer, found that the values for myasthenic patients were lower than normal and concluded that the causative factor in myasthenia gravis was not excessive cholinesterase activity. In a subsequent publication Stedman and Russell (1937) confirmed and amplified these observations in a series of 12 cases of myasthenia gravis. Later, Jones and Stadie (1939), using the Warburg respirator, were unable to detect any significant change from normal in the one case of myasthenia gravis which they studied.

The volumetric method consists in estimating the amount of sodium hydroxide required to neutralize the acetic acid [illegible]

[1] Received May 24, 1943.

acetylcholine by the esterase of the serum over a definite period of time. The period of time employed varies with different investigators. Thus, Gilman, Carlson, and Goodman (1939) made their observations during five minutes, Hall and Lucas (1937) during 10 minutes, while McGeorge (1937) employed a period of 20 minutes, and Butt, Comfort, Dry, and Osterberg (1942) 30 minutes. Goodman, Carlson, and Gilman (1939) found in their one case an abnormally high level of serum cholinesterase activity, whereas McGeorge (1937) in three cases and Hall and Lucas (1937) found no significant alteration from normal. Milhorat (1938), using the same method as McGeorge, found in six cases levels well within normal limits. Similar results were found by Poncher and Wade (1939) in a study of two cases.

The biological method used by Hicks and Mackay (1936) consisted in estimating the time taken for the recovery from acetylcholine inhibition of the isolated frog heart perfused with a mixture of acetylcholine and normal or myasthenic serum. They concluded from the two cases which they studied that the cholinesterase level at all times exceeded that of normal, and that the severity of the symptoms was closely related to the esterase activity of the serum. Lackey and Slaughter (1939) did not describe the method used, but found that the values for the two cases observed did not exceed those for normal subjects.

We have examined the serum cholinesterase activity of 14 patients with myasthenia gravis and six normal adults. The serum was withdrawn at various periods of the day and night, and all specimens were taken when the patients were not receiving any medication. We employed a manometric method using a Warburg manometer as described in a previous paper (Stoner and Wilson, 1943). The unit of cholinesterase (QCO_2) represents the amount (μl.) of carbon dioxide evolved from acetylcholine by 1 μl. of serum per hour. All the determinations were done in duplicate and the figures in Table I represent the maximum, minimum, and average values of the number of separate samples of serum tested in each case.

Results. The serum cholinesterase activity of 12 patients with myasthenia gravis fell within the range found in normal persons. In two patients some low values were obtained, the lowest being 1·86 units. In no case did the cholinesterase activity of the serum appear to bear any relationship to the severity of the symptoms and signs. The average value for the serum cholinesterase activity of patients with myasthenia gravis was found to be 4·17 units, while the corresponding value for normal adults was 4·82 units. The standard deviat[illegible] derived from these figures shows that for the former group σ i[illegible] the latter group 1·095.

In the[illegible] with myasthenia gravis Stedman and Russell (1937) obs[illegible] activity in the blood corpuscles of myasthenic [illegible] for normal persons, the tivity in th[illegible] concluded that there was [illegible] the corpuscles and [illegible] tory mechanism

to reduce the amount of cholinesterase available in the tissues for the destruction of acetylcholine.

We have observed (Stoner and Wilson, 1943) that muscular exercise does not produce any significant alteration in the serum cholinesterase activity of either normal adults or patients with myasthenia gravis. *In vitro* studies

TABLE I

Serum Cholinesterase Activity of Patients with Myasthenia Gravis and Normal Adults

Case	Number of samples	Units serum cholinesterase activity: Maximum	Minimum	Average
Patients with myasthenia gravis:				
1	39	3·56	2·02	2·74
2	34	4·93	3·33	4·02
3	23	4·98	3·20	4·26
4	7	5·60	3·91	4·59
5	8	6·26	4·27	5·12
6	13	7·91	5·49	6·55
7	13	4·04	3·48	3·68
8	6	4·40	3·83	4·08
9	8	4·74	3·96	4·16
10	9	3·79	2·65	3·35
11	17	2·44	1·86	2·19
12	4	4·91	4·56	4·67
13	4	4·25	4·19	4·21
14	6	5·46	3·91	4·81
Standard deviation	1·098		Mean 4·17	
Normal adults:				
15	4	6·34	4·20	5·16
16	4	3·92	3·03	3·48
17	4	6·27	5·86	6·09
18	4	3·79	3·41	3·57
19	4	5·20	5·10	5·16
20	4	5·85	5·17	5·45
Standard deviation	1·095		Mean 4·82	

on prostigmin inhibition of serum cholinesterase activity (Hills and Wilson, unpublished) have indicated that myasthenic serum is not inhibited by prostigmin to any greater extent than is normal serum. It thus appears that myasthenic serum does not differ significantly from normal serum in cholinesterase activity, and there is no evidence that the muscular weakness in myasthenia gravis is due to an excessively rapid destruction of acetylcholine by the enzyme cholinesterase.

Liberation of Acetylcholine at the Neuromuscular Junction

Various attempts have been made to substantiate the hypothesis that the acetylcholine liberated at the myoneural junction is less than normal. Because of obvious technical difficulties, no method has yet been elaborated to estimate the acetylcholine liberated at the neuromuscular junction of patients with myasthenia gravis. Walker (1934) and Cooke and Passmore

(1936) attempted to produce an effect in patients with myasthenia gravis by the subcutaneous injection of as much as 100 mg. of acetylcholine chloride, but were unable to demonstrate any effect. Fraser, McGeorge, and Murphy (1937), however, employing doses of 500 to 600 mg. subcutaneously, reported a definite recovery of muscular power which, though delayed in onset, was sustained till the following morning. They realized that the chief cholinergic action involved was the 'nicotine' effect on skeletal muscle and were able to produce this by the subcutaneous injection of carbaminoyl choline chloride. The effect developed more slowly, but was more prolonged than that produced by prostigmin. It was not, however, so intense or full in its relief of symptoms. They observed that the 'muscarine' action was also produced, resulting in abdominal pain and increased lachrymation, salivation, and sweating. Acetyl-β-methyl choline chloride was also used in doses of 25 and 50 mg. and produced recovery of muscle-power somewhat similar to that effected by acetylcholine chloride, but here again the undesirable 'muscarine' effects on the cardiovascular system were observed. They concluded that the effect of these esters of choline was to elaborate or to assist in the elaboration of a precursor or precursors of acetylcholine, and while they were unable to produce any evidence of such a precursor they were of the opinion that the essential lesion in myasthenia gravis is a defect in the production of acetylcholine.

We were impressed by the toxic effects which occasionally arise from the use of the choline esters and we decided to observe the effect of the subcutaneous injection of gr. 1/10 of pilocarpine nitrate, although it was realized that this drug produces chiefly 'muscarine' effects. The drug was administered to eight patients after the withdrawal of prostigmin and the development of definite clinical signs of myasthenia gravis. The chief effects observed were entirely muscarine-like. Fifteen minutes after injection the patients complained of a feeling of warmth, and vasodilatation of the superficial vessels of the skin of the face, hands, and feet was observed. This was accompanied by sweating and salivation which lasted for about 45 min. Three of the patients complained of palpitation which lasted for 10 min. In two cases lachrymation occurred. In no case was there any recovery of muscle-power nor was there any alteration in ptosis or phonation. It may be argued that the 'nicotine' action of pilocarpine is so weak that no effect on voluntary muscle is to be expected; no contraction of the pupil was observed in any of the cases. Consequently, while of interest, these results do not form a refutation of the argument of Fraser, McGeorge, and Murphy (1937). More recently, Harvey and Lilienthal (1941) have injected acetylcholine into the brachial artery of myasthenic patients and were able to demonstrate, in addition to flushing, sweating, and pain, an involuntary flexion of the fingers, hand, and wrist. In contrast to the findings of Fraser, McGeorge, and Murphy (1937), they were unable by this method of 'close-arterial' injection to produce any lasting improvement in muscle-power. They concluded that there was no primary disorder in myasthenia gravis

because the muscle fibres are capable of vigorous contraction provided that they are adequately stimulated, and suggested that the defect is in the nervous or neuromuscular conduction.

Possibility of a Substance Blocking the Action of Acetylcholine

Several investigators, notably Nevin (1934, 1938), have suggested the possibility of the presence in the blood or tissues in myasthenia gravis of an abnormal substance or metabolite with a curare-like action which raises the threshold of skeletal muscle to the effects of acetylcholine. Walker (1938) tested this theory by occluding the circulation in the upper limbs and exercising the muscles of the forearm. On releasing the constriction an increase in the clinical signs was observed after a latent period of a minute and a half; the effect was more marked after two minutes. She concluded that myasthenic muscles liberate a chemical substance which passes into the circulation and produces a neuromuscular block in the motor end-plates of skeletal muscle. More recently as a result of the beneficial effects resulting from thymectomy, Blalock, Harvey, Ford, and Lilienthal (1941) have suggested that there is a relationship between the thymus and the neuromuscular block present in myasthenia gravis.

We decided to investigate this aspect of the problem by repeating the experiments of Walker. At the outset it appeared to us that some difficulty might be experienced in assessing the alteration of any clinical signs during a period of, say, four minutes. We decided, therefore, to record as many as possible of the objective signs, and we made cine-camera photographs of the patients during the test. In these photographs we hoped to detect any change in facial expression or increase in ptosis. The details of the test were essentially similar to those given by Walker (1938). The test was performed when the patient was not under the influence of prostigmin. The patient was seated in a chair, sphygmomanometer cuffs were attached to both upper arms, and he was allowed to sit at rest while photographs were taken. The sphygmomanometer cuffs were inflated to 200 mm. of mercury and exercise of muscles of the forearm was undertaken immediately and continued for four minutes. The pressure was released and observations and film exposures by the camera were made at intervals of 10 sec. for six minutes after the release of the pressure.

Results. The clinical observations were carried out on 14 patients; cine-camera recordings were made of eight patients. By clinical observation an increase in ptosis was noted in 11 cases during the course of the experiment. Analysis of the cine records, however, showed that increased ptosis occurred in another case in which no change had been observed clinically. The response was thus evident in a total of 12 cases, that is, 86 per cent., of the cases studied. The onset of the response varied in each case; in some it occurred as early as 10 sec. after release of the circulation, while in one case a period of four minutes elapsed before any increased ptosis was evident. These observations confirm the results described by Walker (1938).

In order to elucidate further the effects of exercise of one group of muscles on the fatiguability of another group, we decided to record the changes graphically by means of a specially constructed ergograph. We experienced at first some of the difficulties encountered by Schlezinger (1940), but after some experimentation a method was evolved whereby the capability of a group of muscles to maintain a constant tension was recorded in the

TABLE II

The Effect of Releasing the Circulation from a Distant Group of Exercised Muscles on the Muscle Tension of the Right Middle Finger of three Patients with Myasthenia Gravis

Case	Medication	Time		Surface area	
		Control C_2/C_1	Experiment E/C_3	Control C_2/C_1	Experiment E/C_3
1	No prostigmin effect	1·11	0·80	1·0	0·60
6	" " "	1·0	0·50	0·77	0·57
9	" " "	1·0	0·21	1·10	0·11
1	1 hr. after 2·5 mg. prostigmin subcutaneously	1·0	0·43	1·2	0·88
6	1 hr. after 15 mg. prostigmin orally	1·0	1·30	1·0	4·00
9	1 hr. after 15 mg. prostigmin orally	0·91	0·66	0·9	0·66

manner outlined below. The right hand and forearm were immobilized on a dorsal plaster slab in such a manner as to leave the middle finger free. A loose-fitting thimble was fitted over this finger extending to the proximal interphalangeal joint. The thimble was attached by means of a hook to a wire which, after passing over a series of pulleys, was connected to a solid cylindrical rod of exactly one kilogram weight. A pointer was fitted to the base of this cylinder so that all movements of the cylinder were recorded on a drum moving at a known speed. To obtain a tracing, the finger was flexed at the metacarpophalangeal and the proximal interphalangeal joints and the thimble was placed on the finger. The wire was attached to the thimble and the recording drum set in motion. A tracing was then obtained as the finger, gradually becoming exhausted, extended until the finger and wire were in line, at which point the thimble slipped off. In assessing the fatiguability of the muscle two aspects of the tracing were studied.

(1) The time taken between the initiation of the tension and the point at which the thimble slipped off.

(2) The surface area of the 'triangle' formed by the path of the pointer travelling from the starting point to the point at which the thimble slipped off (Fig. 1).

The experiment was conducted as follows. At a definite time after the last dose of prostigmin two control tracings, C_1 and C_2, were made at an interval of six minutes. Later, at a similar time after the last dose of prostigmin, a sphygmomanometer cuff was attached to the left arm and a further control tracing, C_3, taken. The sphygmomanometer cuff was then inflated to a

pressure of 200 mm. of mercury for a period of four minutes during which exercise of the forearm muscles was undertaken. After four minutes the cuff was deflated, and two minutes later a fourth tracing E was recorded.

Results. Observations were made on three patients in the absence of any prostigmin effect and at stated intervals after the administration of prostigmin. The results are expressed in Table II where the third column

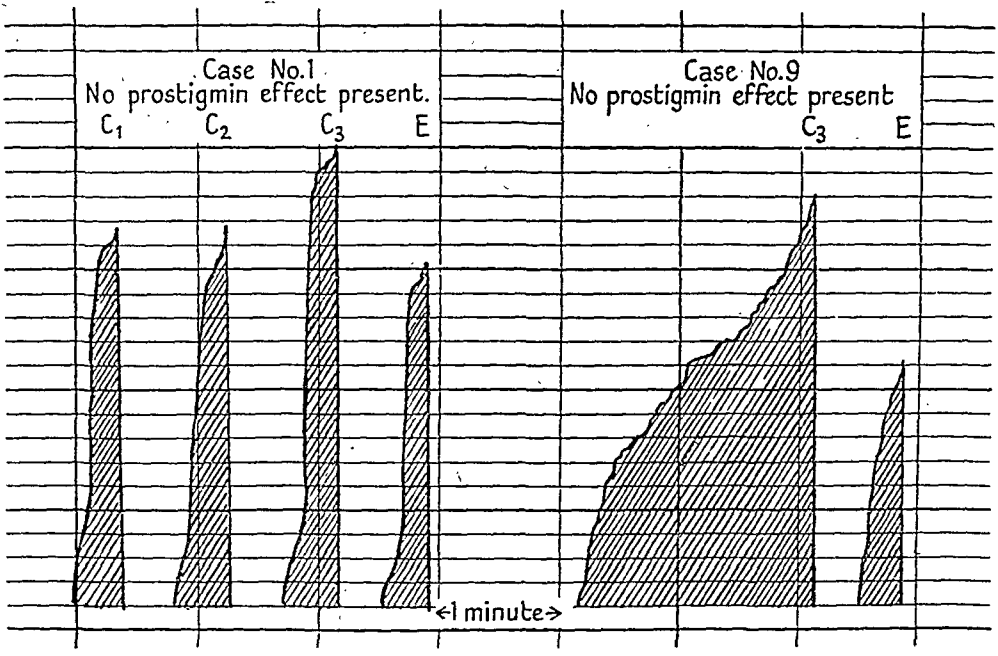

FIG. 1. Ergograph tracings from two cases of myasthenia gravis (Cases 1 and 9) showing the effect of exercise of a remote group of muscles on the fatiguability of the flexor muscles of the right middle finger. C_1, C_2, and C_3 = control tracings. E = tracing taken two minutes after exercise. In Case 9, in order to save space, C_1 and C_2 have been omitted.

(C_2/C_1) represents the control observation and in the fourth column the ratio E/C_3 indicates the effect on muscle tension of release of the circulation from the distant group of exercised muscles.

In the three subjects studied, when no prostigmin effect was present exercise of the remote group of muscles produced an increase in the fatiguability of the finger muscles, as indicated by a marked decrease in the time during which the weight was sustained and in the surface area covered by the tracing (Fig. 1). These records serve to support the clinical and cine-camera observations already described. We have already shown (Stoner and Wilson, 1943) that this effect is not due to an increase in the cholinesterase activity of the serum.

When the observations were carried out during medication with prostigmin, the effect on the fatiguability of the muscle seemed to depend on the route and time of administration of the drug. Thus in Cases 6 and 9, when the records were taken one hour after 15 mg. by mouth there was a very marked decrease in muscle fatiguability, whereas Case 1 after 2·5 mg. subcutaneously

showed a marked increase in fatiguability. It is difficult to explain why Case 1 was unable to sustain the weight for a longer period, though it was noted that about this period his clinical response to the injection of prostigmin was not always satisfactory. From the results of Cases 6 and 9 it is obvious that prostigmin interferes with or modifies the action of the circulating substance.

It appears to us that there are two possible explanations of this phenomenon. Firstly, prostigmin by virtue of its anti-esterase activity enhances the action of the transmitter substance, acetylcholine, by enabling it to act for a longer period, and the addition in such circumstances of the same amount of circulating substance generated by exercise is not so obvious as in the muscle already fatigued. The whole action of prostigmin could then be explained in terms of its anti-esterase activity. On the other hand Briscoe (1936) and Cowan (1938) have shown experimentally that prostigmin can reverse or antagonize the action of curare. If the effects which we have observed are due to the presence of a curare-like substance, then part of the action of prostigmin could be accounted for by its ability to counteract the substance and raise the threshold of the muscle to a normal excitation level.

We decided to test the serum of these patients for the presence of a substance with a curariform action. In our earlier experiments the isolated gastrocnemius-nerve preparation of the frog was used, but later we employed the isolated sartorius as being more sensitive. The isolated gastrocnemius with its nerve was mounted in a Lucas trough filled with frog Ringer's solution at a temperature of 14 to 16° C. and stimulated through a pair of platinum wire electrodes, 1 mm. apart, the stimulus applied being derived from a Du Bois Reymond coil. In our later experiments, with the sartorius preparation, the method of Cowan (1938) was employed, the only modification being that in some experiments, instead of using non-polarizable electrodes we used platinum wires as above. The stimulation was effected by means of the time-base of a cathode ray oscillograph. This is fundamentally similar to a neon tube stimulator except that the neon tube is replaced by a gas-filled triode valve. The arrangement enables greater control of stimulating potential and frequency. The frequency was standardized against the 50 cycle mains by means of the oscillograph. After the preparation had been allowed to soak for an hour in the perfusion fluid, records were obtained by stimulating the nerve every 10 min. for 0·15 sec., using a frequency of 50 stimuli per second and an amplitude sufficient to give just submaximal shocks. The duration of stimulation was controlled by a make and break contact operating from the revolving drum. The time of stimulation was constant throughout. Control records were taken until three consistent responses were obtained. The serum (1 c.c.) was then added directly to the bath and the preparation was stimulated approximately every 10 min. during the next 140 min. The serum employed was separated and used within three hours of withdrawal from the patient. Except where indicated, blood was taken from patients at a time when they were not under the influence of prostigmin. The

following specimens of blood-serum were examined in this way—serum from patients with myasthenia gravis withdrawn during occlusion of the circulation before exercise, and during occlusion of the circulation after exercise as described above; and serum from normal persons withdrawn under the same conditions as that from the myasthenia patients.

Results. The serum from 13 patients with myasthenia gravis was tested in the above manner as well as the serum from six normal persons. Using

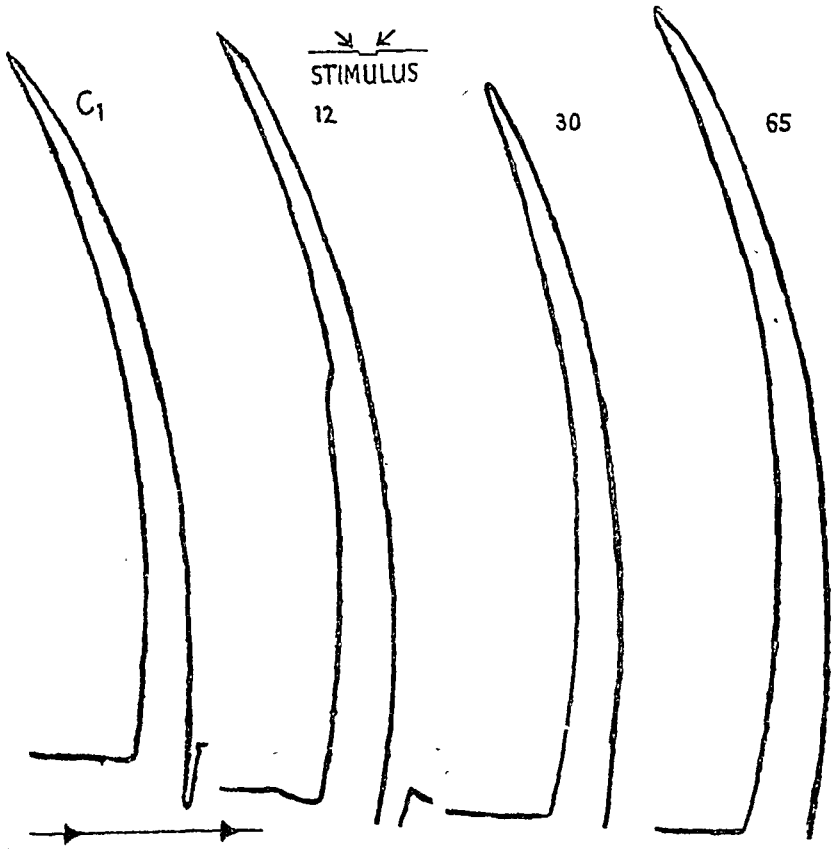

FIG. 2. The effect of normal serum, withdrawn after exercise, on the contraction of the isolated frog sartorius muscle preparation following nerve stimulation. C_1 = control tracing. Records taken 12, 30, and 65 minutes after the addition of serum. Stimuli—submaximal shocks at 50 per sec. for 0·15 sec. Time tracing between signal = 1 sec.

serum from the normal group we were unable to detect any change in the height or configuration of the muscle contraction after nerve stimulation (Fig. 2). In the myasthenia group 11 patients showed a depression of the normal muscle contraction. The depression varied in individual cases from 10 per cent. to almost 100 per cent. and was manifest from eight minutes onwards. In the group before exercise the depression of muscle contraction was never greater than 25 per cent. In the experiments with the serum taken after exercise the depression produced in some cases increased until there was no response to nerve stimulation (Fig. 3). After the depression

to nerve stimulation had been manifest all the preparations responded to direct muscle stimulation. Replacement of the perfusion fluid by Ringer's solution did not restore immediately the muscle contraction to the previous control level.

In another series of experiments the nerve was stimulated with submaximal shocks at a frequency of 150 per sec. for 15 sec. in an endeavour to explore

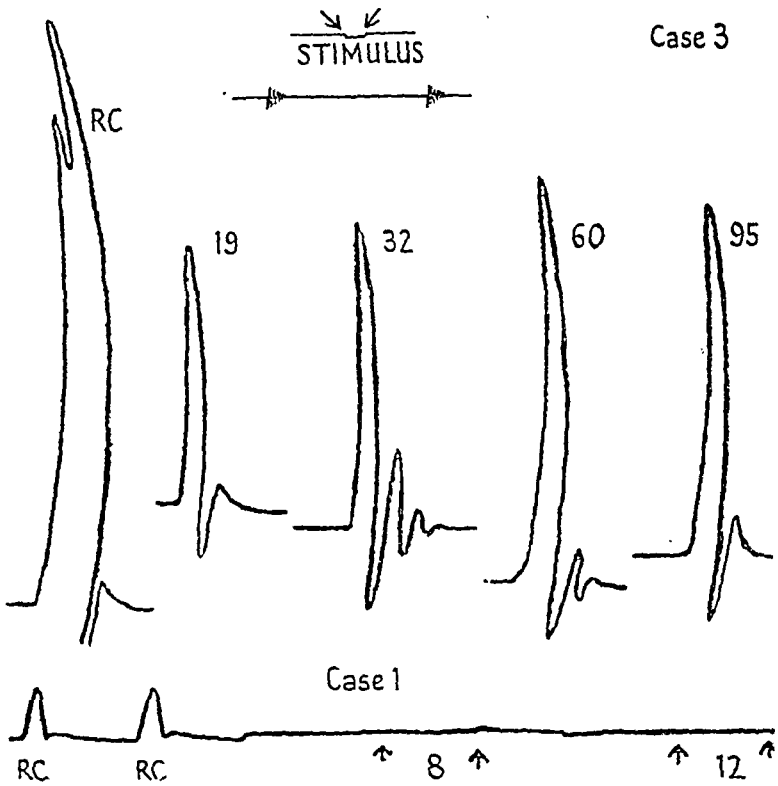

FIG. 3. The effect of myasthenic serum taken after exercise on the contraction of the isolated frog sartorius muscle preparation following nerve stimulation. RC = control tracings. Numbers indicate time in minutes after addition of serum. Stimulation as in Fig. 2. Time tracing between signal = 1 sec.

the effects of serum on the tetanic contraction of the nerve-muscle preparation. Ten minutes after the addition of the serum (collected after exercise and in the absence of prostigmin) an appreciable decrease in the maximum tension was observed (Fig. 4). Thirty minutes later the initial rise was further diminished though the tension was sustained for 12 sec. before the muscle was fatigued. Seventy minutes after the addition of the serum the preparation appeared to have recovered, as the response to nerve stimulation closely resembled the initial control level.

The effect of the addition of another specimen of serum was evident within seven minutes and in 12 minutes only a very small contraction was produced, which, however, was sustained throughout the period of stimulation (Fig. 5). Immediately after washing the preparation several times with

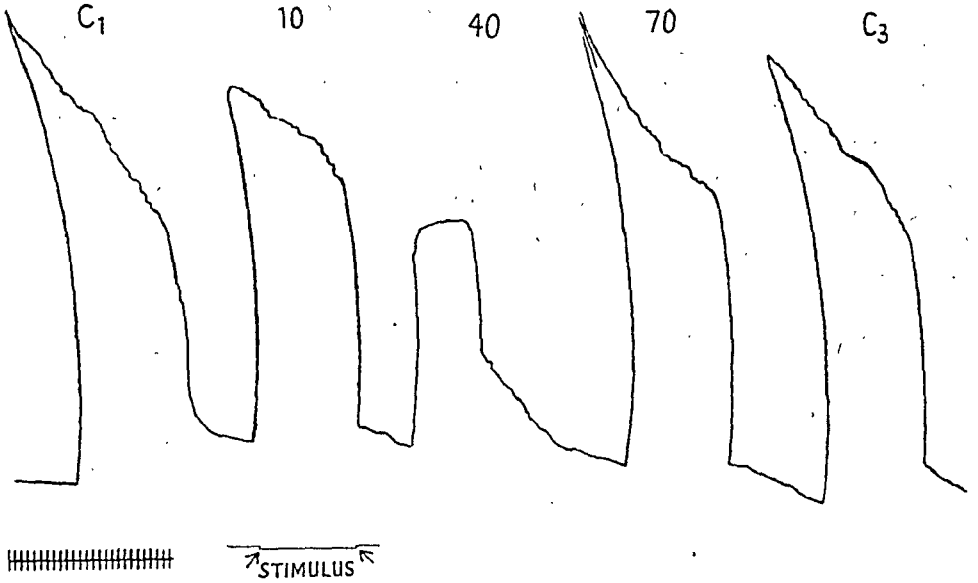

FIG. 4. The effect of myasthenic serum taken after exercise on the contraction of the isolated frog sartorius muscle preparation. Nerve stimulated for 15 sec. with 150 submaximal stimuli per second. C_1 and C_3 = control tracings. Numbers indicate time in minutes after the addition of serum. Speed of drum 1 mm. per second. Time tracing between signal = 1 sec.

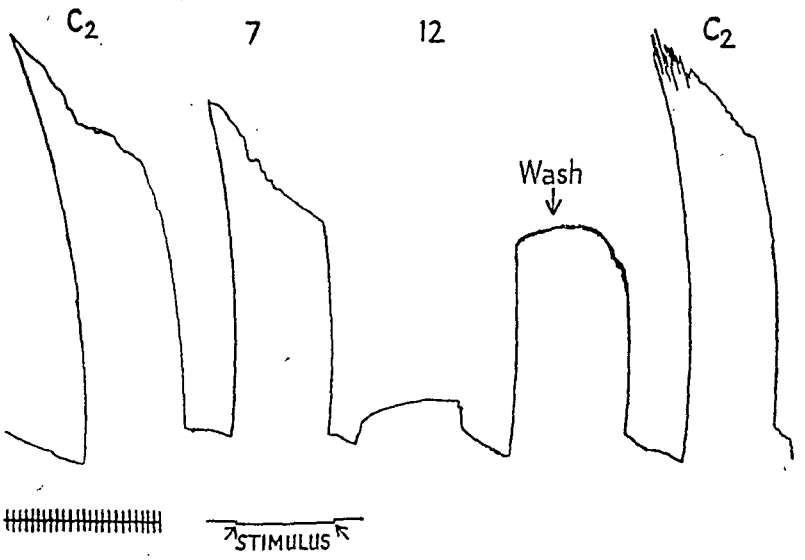

FIG. 5. The effect of myasthenic serum taken after exercise on the contraction of the isolated frog sartorius muscle preparation. Nerve stimulated as in Fig. 4. C_2 = control tracings before and after addition of serum. Numbers indicate time in minutes after the addition of serum. Wash = after washing preparation with Ringer's solution. Speed of drum 1 mm. per second. Time tracing between signal = 1 sec.

Ringer's solution there was a partial recovery of the muscle response and 20 min. after washing with Ringer's solution the response to nerve stimulation was equivalent to the original control record.

In view of the observations of Briscoe (1936, 1937) and Cowan (1938) already quoted, we tested the serum after exercise from four patients one hour after they had received 1·5 mg. of prostigmin and 1 gr. of ephedrine hydrochloride subcutaneously. We found that whereas in the absence of any medication their serum, withdrawn after exercise, produced some neuromuscular block, no such effect was now seen. These clinical and experimental observations appear to support the contention that there is in the blood of patients with myasthenia gravis a substance which produces a block in neuromuscular transmission, and further that prostigmin exerts some action which neutralizes or inhibits the action of this substance.

Discussion

Myasthenia gravis is a disease which may be manifest at any age. While Kennedy and Moersch (1937) and Viets and Schwab (1939) have described the age of onset as ranging from 10 to 77 years, isolated case reports provide evidence of the disease in one infant of 21 months (Kawaichi and Ito, 1942) and in another infant aged 23 months (Booth, 1908). The possibility of its occurrence in a new-born child is shown from the report of one of our own cases (see Appendix). While there is apparently some evidence that the condition may be hereditary (Brain, 1940), the bulk of the evidence is against this view. It is true that the new-born infant which we observed had very marked symptoms during the first two weeks of its life, but we are of the opinion that these symptoms were due to intra-uterine influences, because careful examination from time to time has failed to reveal any evidence of the disease after this period. Another of our patients (Case 1) who was very severely affected has a uniovular twin brother who is quite free from the condition.

The only predisposing factor which we could elicit was an emotional disturbance just prior to the time of onset of the first symptom. This we observed in four cases. The effect of emotion in increasing the severity of established symptoms has already been reported (Price, 1941).

The influence of climatic conditions on the disease has been described by Edgeworth (1933) who, suffering from myasthenia gravis, found that during periods of intense heat in the summer she required to take more ephedrine to prevent prostration. Our attention was drawn in one patient to a sudden increase in the severity of his condition during a hot sunny day. We followed up this observation in all the patients and found that in eight cases they avoided exposure to sunlight and stated that unless they sat in the shade they became very weak, and ptosis, diplopia, and dysphagia developed quickly. We were able to confirm these statements by placing these patients in the sunshine. We noted that while there was evidence of increased fatiguability of the voluntary muscles, in no instance was there any weakness of the circular muscle fibres of the iris. Exposure to heat from electric or coal fires did not

have any effect on the condition. It would be interesting to know which particular wavelengths of light are responsible for this curious phenomenon.

Myasthenia gravis seldom begins as a generalized process, but remains localized for a period to one or two groups of voluntary muscles. The characteristic weakness and rapid fatiguability may begin in the muscles of the eyes, face, pharynx, palate, limbs, neck, or trunk. The presenting symptoms in our patients were diplopia (four cases), ptosis (four cases), weakness of arms and legs (four cases), and difficulty in chewing (two cases). In most cases the symptoms developed fairly rapidly and were well established in a period which varied from six weeks to six months. One of our cases formed an exception, as there was a delay of about five years before the increase in symptoms was fully developed. The question of remission figures largely in most descriptions of the disease, but it has been our experience that remissions are by no means a constant feature. It is true that there is often fluctuation in the severity of the condition, but there usually remain some manifestations of its presence. Probably the most exhaustive account of this feature of the disease is given by Viets, Schwab, and Brazier (1942) who compared the remission experienced during the first and second trimester of pregnancy with that which occurs in the natural course of the disease. According to these authors the remission during pregnancy is much more complete and is like the 'sense of well-being experienced after an injection of prostigmin methylsulphate, only prolonged over days and months instead of lasting a few minutes'.

Only one of our patients (reported in the Appendix) has become pregnant since the onset of the disease and in this case pregnancy has occurred on two occasions. During the course of the pregnancies her symptoms remained unchanged. In this patient, as in many instances in the literature, labour appeared to be normal and had no serious effect upon the disease. Only one case (No. 9) showed evidence of thyroid enlargement, but there was no indication of any thyrotoxicosis. There was no evidence in any of the cases of disturbance of the lymphatic system as judged by the absence of enlargement of the lymphatic glands or the spleen; the peripheral blood showed no increase in the number of lymphocytes. Much attention has recently been focused on the role of the thymus in myasthenia gravis. Post-mortem examination of patients with myasthenia gravis has shown that about 50 per cent. of cases have hyperplasia, tumour, or persistence of the thymus (Norris, 1936). There is little, if any, evidence that such abnormalities have been detected in the living patient. We took the opportunity of examining all our patients for enlargement of the thymus by both clinical and radiological means. In no instance were we able to detect any thymic enlargement. In view of the condition of the thymus found at operation in the cases reported by Blalock, Harvey, Ford, and Lilienthal (1941) and Carson (1943) it appears that clinical and radiological studies are of no value in determining the condition of the thymus.

That there is a striking resemblance between myasthenia gravis and the

early stages of curare poisoning has already been pointed out by Nevin (1938), Walker (1934), and others. The experiments described in the present paper indicate that in the blood of patients with myasthenia gravis there is a substance which under certain conditions will produce an exacerbation of the signs and symptoms of the disease. If the substance is circulating in the blood it is difficult on the one hand to explain why certain muscles are

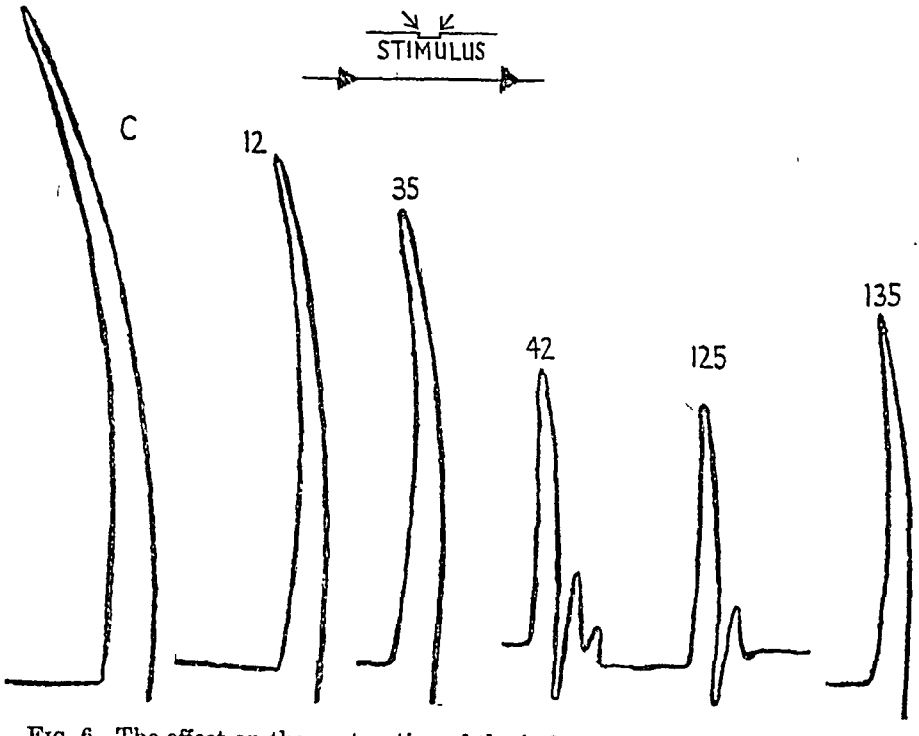

FIG. 6. The effect on the contraction of the isolated frog sartorius preparation of an alcoholic extract of 3 c.c. of myasthenic serum (Case No. 3) withdrawn after exercise. C = control tracing. Records taken 12, 35, 42, 125, and 135 minutes after the addition of the extract. Stimulation as in Fig. 2. Speed of drum 25 mm. per second. Time tracing between signal = 1 sec.

Note.—The extract was prepared by adding 3 c.c. of serum to 12 c.c. of absolute alcohol. The precipitate was removed and washed with absolute alcohol. The alcoholic solution was evaporated to dryness *in vacuo*. The residue was dissolved in Ringer's solution, filtered and added to the perfusion bath. Extracts of normal serum did not produce any effect.

firstly and chiefly affected; yet on the other hand it is possible that there is a difference in the density of innervation of these muscles so that any disturbance in the muscle response to acetylcholine, brought about by the circulating substance, would be more readily detected in these muscles than in others. Whether the circulating substance produces its effect by decreasing the amount of acetylcholine available to the effector or whether it raises the effector's threshold of response to acetylcholine is a matter which can be settled only by further investigation.

The dramatic response of the patient with myasthenia gravis to prostigmin is universally recognized. If the action of prostigmin is entirely accounted

for by delaying the hydrolysis of acetylcholine, one must assume that the amount of acetylcholine produced in the myasthenic patient is sufficient to effect a normal contraction of muscle, provided that the cholinesterase activity is inhibited. There is no evidence that the 'muscarine' action of acetylcholine is deficient in these patients in the absence of prostigmin, for they exhibit all the normal signs of secretion controlled by cholinergic nerve fibres, and the experiments with pilocarpine confirm this observation. It thus appears that something interferes with the normal action of acetylcholine on the voluntary muscles and that the disturbance is more probably due to an alteration in the threshold of response to acetylcholine than to a deficiency in the synthesis of acetylcholine. It seems to us possible that part at least of the action of prostigmin in the myasthenic patient may be to produce some antagonistic effect on the inhibiting substance which we have described, and thereby restore the normal threshold of the effector to acetylcholine.

We have as yet no evidence of the exact chemical nature of the substance. It appears to be partially soluble in alcohol (Fig. 6) and the serum becomes inactive after being stored in the refrigerator for 24 hours. It is possible that the thymus gland may play an integral part in the secretion or control of the substance, as the recent investigations of Harvey, Lilienthal, and Talbot (1942) suggest. As the clinical history of the son of Case 8 indicates, the substance probably results from some fundamental metabolic disturbance. During the first fortnight of his life he presented the typical features of a severe case of myasthenia gravis. Yet he is now, in the absence of any treatment, quite a normal healthy child. This may be an instance of a complete remission, but on the other hand we are inclined to hold the view that once the child began to lead a separate existence something which caused this condition was removed from his metabolism. It is logical to assume that the source lay in the maternal myasthenic blood and that two weeks elapsed before this substance was removed from the infant's blood-stream. It is further noteworthy that his mother, before she had myasthenia gravis, gave birth to a normal healthy child. We consider that the most probable explanation, at present, of the phenomenon of myasthenia gravis is the presence of some substance in the blood which produces a block in neuro-muscular transmission and inhibits the normal action of acetylcholine on voluntary muscle.

Summary and Conclusions

The following conclusions are based on a study of 14 cases of myasthenia gravis; the report includes a record of the occurrence of the disease in a newly born infant.

1. The serum cholinesterase activity of patients with myasthenia gravis is not greater than that of normal adults. There is no evidence that the muscular weakness in myasthenia gravis is due to an excessively rapid destruction of acetylcholine by cholinesterase.

2. Patients with myasthenia gravis are able to synthesize acetylcholine in sufficient amounts to produce the normal 'muscarine' effects on glands and

involuntary muscle. These effects have been increased by the administration of pilocarpine.

3. Exposure to sunlight causes an increase in the severity of the symptoms and signs.

4. By means of cine-camera and ergograph studies it has been shown that exercise of a remote group of muscles produces an increase in the severity of the signs.

5. The serum of patients with myasthenia gravis not under prostigmin treatment, when tested on the isolated nerve-muscle preparation of the frog, produces a block in neuromuscular transmission. This effect is not obtained with serum collected from patients during prostigmin treatment.

6. The blood of patients with myasthenia gravis contains a substance, partially soluble in alcohol, which interferes with neuromuscular transmission. The role of this substance in the causation of myasthenia gravis is discussed.

We wish to express our thanks to Professors J. H. Gaddum and E. J. Wayne for helpful criticism and to Drs. E. Eaves, K. J. G. Milne, and J. Pemberton for their co-operation. For clinical facilities and access to the cases under their care we wish to record our gratitude to Professor E. J. Wayne, Dr. A. G. Yates, Honorary Physicians to the Sheffield Royal Infirmary, to Dr. D. H. Collins, Medical Superintendent of an E.M.S. Hospital, and to the Medical Superintendent of the City General Hospital. We are indebted to Mr. I. G. H. Page for valuable assistance in the construction of the cathode ray oscillograph apparatus, and to Dr. C. H. Browning for assistance in the dissection of the frog muscle preparations. It is a pleasure also to acknowledge our appreciation to Mr. E. Salvin for technical assistance. The expenses of this work were partially defrayed by a grant from the Medical Research Council.

Appendix

Case 8. A housewife, aged 25 years, was first seen in January, 1939, complaining of drooping of both eyelids, variable diplopia, and weakness of the legs and arms. A year previously she had given birth to a live male child which has since developed normally. Six months after the confinement her left eyelid drooped at night and she began to experience weakness of the legs and arms. She had attacks of diplopia and nuchal pain. On admission to hospital very few clinical features of myasthenia gravis were elicited. After three days' treatment on quinine she was unable to masticate her food and her speech became nasal in character. Diplopia and ptosis were easily produced by a few repeated movements of the eyes from left to right. At this stage there was a dramatic response to the subcutaneous injection of 1·5 mg. of prostigmin.

In 1940 she became pregnant and the pregnancy continued to term without incident or remission of the myasthenia gravis, and in February 1941 she was delivered of a live female child of about six pounds in weight. The labour was very short and at no time did she experience true labour pains. During the labour she had several attacks of breathlessness. There was no

abnormal loss of blood and the uterus contracted down well after delivery. The child never cried and made only feeble attempts at sucking. It was unable to swallow and made only slight movements with face and tongue. There was no ptosis or abnormal ocular movements. Respirations were poor and the child died after four days.

Six months later she again became pregnant. She was adequately maintained on the same daily dosage of prostigmin (135 mg. by mouth) and the pregnancy continued to term, culminating in a normal delivery. The labour lasted for three hours during which she experienced true labour pains. A live male child was born weighing 6 lb. 12 oz. The child did not cry and made only feeble movements with his tongue; his condition closely resembled that of the previous infant. Sucking and swallowing were very poor and milk often regurgitated through his nose. The general movements of the child were weak and respiratory excursions limited. At this time areas of cyanosis were noted on the head and lips. The child lost weight rapidly till he was only 5 lb. 4 oz. After careful feeding his condition gradually improved and at five weeks his weight was 7 lb. 1 oz. No prostigmin was administered. When last seen in January 1943 the child had the appearance and movements of a normal child of his age. In neither the second nor the third child was there any evidence of congenital morbus cordis or of any intracranial damage.

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Case 10

Before release of circulation | 15 sec. after release | 60 sec. after release | 2 min. after release | 6 min. after release

Case 11

Before release of circulation | 10 sec. after release | 60 sec. after release | 3 min. after release | 4½ min. after release

FIG. 7. The effect of exercise of a remote group of muscles on the facies of patients with myasthenia gravis. The circulation in both forearms was occluded by inflating the sphygmomanometer cuffs to 200 mm. of mercury. Exercise of the muscles of the forearm was continued for 4 min. Photographs were taken during exercise and at the intervals stated after the release of the circulation.

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SERUM-IRON IN HEALTH AND DISEASE[1]

By JOAN F. POWELL
(From the Nuffield Department of Clinical Medicine, Oxford)

Introduction

It is generally agreed that iron is present in serum in the form of iron-protein complexes, being non-dialysable, and only a small fraction appearing in the protein-free filtrate after treatment with trichloracetic acid. Vannotti and Delachaux (1942) have measured this fraction in a number of normal and pathological conditions and have suggested that it represents iron present in an active, loosely bound form.

Determinations of total iron have been made on whole serum and plasma after ashing (Moore, Arrowsmith, Quilligan, and Read, 1937), but these methods are rather long and frequently involve a separate determination of haemoglobin iron, since it is not always possible to avoid haemolysis. Alternative methods entail preliminary treatment of the serum with mineral acid to detach the iron from its complexes, followed by protein precipitation and analysis of the protein-free filtrate (Heilmeyer and Plötner, 1937; Barkan, 1937; Vahlquist, 1941). In Heilmeyer's original method, the iron in the protein-free filtrate is reduced to the ferrous state, and determined colorimetrically with ortho-phenanthroline. The results thus obtained have been criticized by Vahlquist (1941) on the grounds that, under Heilmeyer's conditions, complete reduction is not effected. Vahlquist has defined the optimum conditions for reduction and has obtained higher figures than those given by the original method.

Since it is easier to convert all the iron in the protein-free filtrate to the ferric state, this has been the procedure adopted in the present study, the ferric iron being determined by reaction with thiocyanate. This slightly simpler modification of Heilmeyer's method has been used to determine serum-iron values in 70 normal controls (35 male and 35 female) and in patients with various types of anaemia before and during treatment. No attempt has been made to measure the small, variable fraction of serum-iron which appears in the protein-free filtrate on direct treatment with trichloracetic acid. Since the latter is in fact a strong acid (dissociation constant $1{\cdot}3 \times 10^{-1}$), this fraction cannot be taken to represent iron in a loosely bound form, and its significance is doubtful.

Method

All-glass syringes with stainless steel or platinum-iridium needles are used for the collection of blood. After standing for one hour at room temperature,

[1] Received July 26, 1943.

the specimen is centrifuged and the serum separated. As soon as possible after use, the syringe and needle are thoroughly washed with glass-distilled water and dried with alcohol and acetone.

The reagents are, of course, required to be iron-free.

To 4 c.c. of serum, 2 c.c. of 6 N. hydrochloric acid are added. The mixture is stirred with a glass rod and allowed to stand for 15 minutes. Four c.c. of 20 per cent. trichloracetic acid are then added with shaking and, after a further 10 minutes' standing, the mixture is centrifuged and filtered.

Five c.c. of filtrate are transferred to a Pyrex test tube and 0·2 c.c. of concentrated nitric acid added. After heating in the water bath for ½ hour, the solution is cooled, made up to approximately 10 c.c., and 5 c.c. of amyl alcohol followed by 2 c.c. of 3 N. potassium thiocyanate are added. The tube is then shaken thoroughly and the contents allowed to settle. The coloured amyl alcohol layer is measured in a Pulfrich photometer, using 1 cm. cell and filter S 53. For greater accuracy of measurement at very low concentrations, micro-cells of length 5 cm. may be used.

Ferrous ammonium sulphate, oxidized by potassium permanganate, is taken as standard (Knecht and Hibbert, 1918). For the calibration curve, quantities of diluted standard containing respectively 1 to 6 micrograms of iron together with 1 c.c. of 6 N. hydrochloric acid and 2 c.c. of 20 per cent. trichloracetic acid are treated in the above manner.

Duplicate estimations on the same specimen of serum agreed to within 3 per cent., as did also estimations of two separate specimens from the same subject. This latter observation formed a good check on the cleanliness of apparatus, the importance of which has been sufficiently stressed by other workers. Iron added to serum as ferric ammonium sulphate could be recovered with an accuracy of ± 5 per cent., which was thought adequate for the present investigation.

With regard to the question of haemolysis, it was found that the addition of packed red cells to the serum, giving a much greater degree of haemolysis than was actually found in practice, had apparently no effect on the final result. It seems, therefore, that the easily split-off iron of red cells does not become detached under the conditions of the estimation. This has also been observed by Vahlquist (1941).

To obtain a clear liquid after protein precipitation, it was usually found that both centrifugation and filtration were necessary. No loss of iron could be detected during filtration (Schmidt, 1940; Vannotti and Delachaux, 1942).

The properties of the ferric thiocyanate colour have been thoroughly investigated by Moore, Minnich, and Welch (1939). Under controlled conditions the colour intensity is proportional to the concentration, and is stable for one hour in the dark. It is also apparently unaffected by concentrations of phosphate up to five times those normally present in serum.

Results

The serum iron values of 70 apparently healthy subjects (all with haemoglobin 85 per cent. and upwards) expressed as micrograms (γ) per 100 c.c. of serum are summarized in Table I, and compared with values obtained by

other workers. A single value for each subject, the first obtained, was used in the calculation.

TABLE I

Serum Iron of 70 Normal Subjects, Compared with Values Obtained by Other Workers

Authors	Men			Women			Difference
	Number of observations	M ± εM	σ	Number of observations	M ± εM	σ	D ± εD
Heilmeyer and Plötner (1937)	25	126·2 ± 4·3	21·4	25	88·5 ± 3·8	18·8	+37·7 ± 5·7
Moore, Arrowsmith, Quilligan, and Read (1937)	15	121·5 ± 6·7	25·8	15	97·6 ± 6·1	23·7	+23·9 ± 9·1
Vahlquist (1941)	50	142·0 ± 6·1	43·0	50	123·0 ± 4·5	31·6	+19·0 ± 7·6
Present investigation	35	143·0 ± 4·1	24·0	35	117·0 ± 4·5	26·5	+26·0 ± 6·1

M = Mean. εM = Mean error of mean. D = Difference.
εD = Mean error of difference. σ = Standard deviation.

With regard to individual variability, Heilmeyer and Plötner (1937) have found variations of − 10 to + 19 micrograms per cent. in six normal subjects during a period of one to nine days. Similar observations have been made by Skougè (1939) and Vahlquist (1940). The latter author has also obtained evidence for a diurnal variation, serum-iron values in 30 normal subjects at 6 p.m. being significantly higher than those obtained at 8 a.m. on the same day. There appears to be some doubt as to the effect of menstruation on the serum-iron of normal women. Moore, Minnich, and Welch (1939) concluded from analysis of three to six blood specimens obtained from each of 16 subjects during a six months' period that spontaneous variations of 18 to 64 micrograms per cent. do occur, but that these changes are 'oscillating in type and have no persistent directional characteristics'. Hemmeler (1939), however, has defined a normal range of 80 to 100 micrograms per cent. for menstruating women, while for non-menstruating women he has found the range to be the same as that for men, that is, 100 to 130 micrograms per cent. In the present investigation, the analysis has been extended to determine the effect of menstruation. Fifty-five determinations have been made on 28 of the normal women included in the series, and the results classified into four groups, corresponding to the four weeks of the menstrual cycle. The means and standard deviations of these groups were:

	Mean	Standard deviation	Number of estimations
1st week (during menstruation)	100	27	16
2nd week	118	25	12
3rd week	124	17	11
4th week	131	23	16
2nd, 3rd, and 4th weeks together	125	22	39

The numbers of subjects above and below the combined mean were further arranged to form a contingency table. Yates's (1934) modification of the

χ^2 test gave $p(\chi^2)$ considerably less than 0·01. The test was also applied to the complete and more homogeneous data which were available from six of these subjects. The mean values were:—

1st week	99	micrograms per cent.
2nd week	124	,, ,,
3rd week	123	,, ,,
4th week	132	,, ,,

In this case $p(\chi^2)$ was slightly greater than 0·01, still very significant in spite of the reduction in quantity of data, indicating considerable likelihood of a real periodicity in the serum-iron level of normal women.

Serum-iron levels obtained before treatment from patients with various types of anaemia are summarized in Table II. They are on the whole in agreement with those reported in similar conditions. The rather low values obtained in haemolytic anaemias will be discussed below.

TABLE II

Serum Iron in Anaemia

Type of anaemia	Number of cases	Range (micrograms per 100 c.c.)	Mean (micrograms per 100 c.c.)
Hypochromic	30	25 to 90	47
Aplastic	7	170 to 340	257
Pernicious	9	178 to 235	210
Haemolytic	12	65 to 210	116

In hypochromic anaemias responding to iron therapy, serum-iron levels in many cases rose as high as 400 micrograms per cent. In two patients a satisfactory response was obtained only after simultaneous administration of vitamin C. The complete data on one of these patients are given in Fig. 1. A similar case has recently been reported by Thomas and Harvey (1943). The effect of vitamin C in promoting iron absorption, as indicated by increase in serum-iron levels, has been studied by Moore, Arrowsmith, Welch, and Minnich, (1939). These authors have shown that while ferrous salts are more readily absorbed than ferric, the absorption of the latter may be greatly facilitated by simultaneous administration of vitamin C or other reducing agent, for example, sodium formaldehyde sulphoxalate. It therefore becomes of interest to determine whether the absorption of small doses of iron, such as are reported to be inadequate for satisfactory haemoglobin regeneration (Barer and Fowler, 1941) may be improved by the addition of vitamin C. A summary of the serum-iron values found in six cases of hypochromic anaemia before treatment, during treatment with small doses of iron, over a control period of 14 days, and finally, after the addition of vitamin C, is found in Table III. Reticulocyte counts and haemoglobin estimations were also made, and the complete data on one patient are represented in Fig. 2.

The reduction of ferric iron and its maintenance in the ferrous state during its passage into the upper part of the small intestine therefore appears to play an important part in iron absorption. That this is not the only factor operating is illustrated by observations made on a woman with

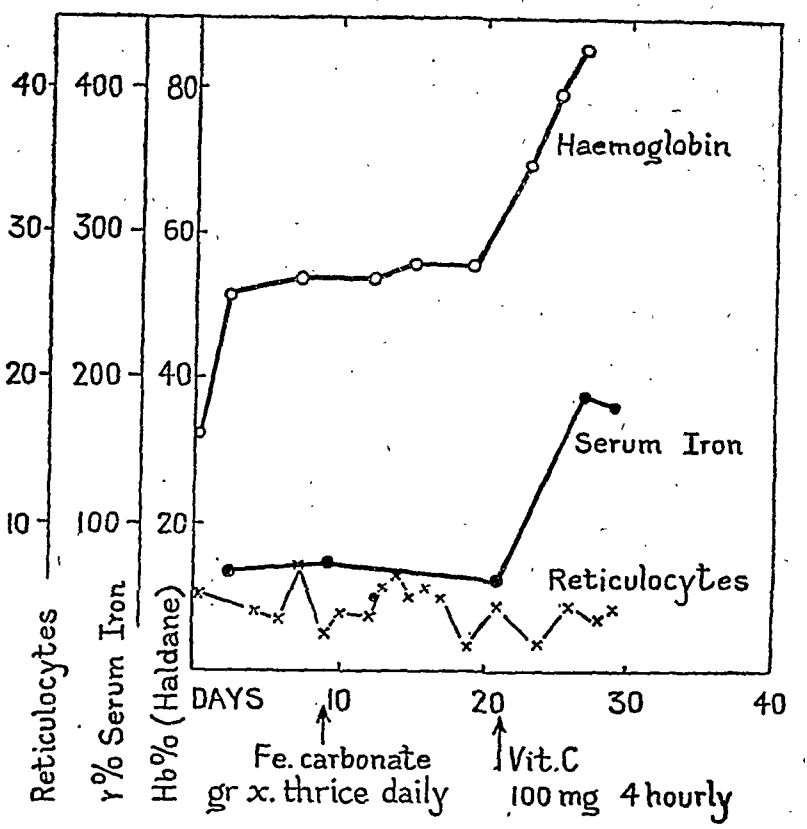

FIG. 1. Response to normal doses of iron before and during addition of vitamin C

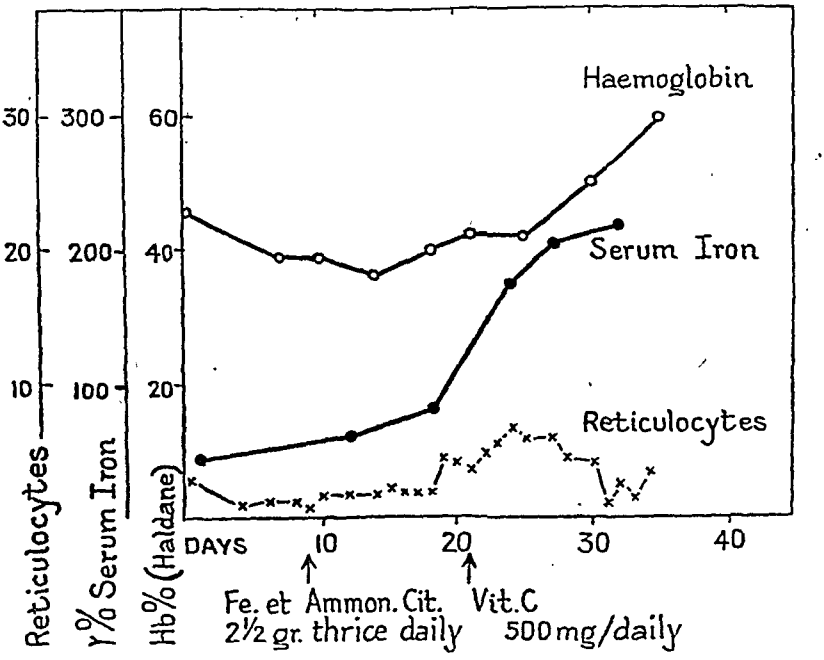

FIG. 2. Response to small doses of iron before and during addition of vitamin C

TABLE III

Effect of Vitamin C on Absorption of Small Doses of Iron in Female Patients

Patient	Fractional test meal	Serum iron (micrograms per 100 c.c.) On admission	During treatment with iron alone	During treatment with iron and vitamin C	Dosage
1	Free hydrochloric acid present	50	170 after 3 days 100 „ 12 „	180	4 gr. Fe. et Ammon. Cit. and 500 mg. vit. C daily
2	Histamine refractory achlorhydria	43 50	45 „ 3 „ 48 „ 6 „	110	7½ gr. Fe. et Ammon. Cit. and 500 mg. vitamin C daily
3	Histamine refractory achlorhydria	30	40 „ 3 „ 30 „ 12 „	190	
4	Free hydrochloric acid present	50 33	75 „ 3 „ 90 „ 10 „	350	
5	Histamine refractory achlorhydria	43	60 „ 2 „	176 205 220	
6	Histamine refractory achlorhydria	55	75 „ 2 „	110 90	

hypochromic anaemia, with haemoglobin 50 per cent. and normal gastric acidity. Here, in spite of intense treatment with iron (ferrous sulphate, gr. 10 five times daily) and vitamin C (100 mg. five times daily) a satisfactory haemoglobin regeneration was not obtained, the haemoglobin rising only to 60 per cent. in one month. Serum-iron levels during this period were never higher than 46 micrograms per cent., and in the specimen obtained three hours after iron and vitamin C administration the value was only 30 micrograms per cent. Specimens of urine obtained during treatment contained large quantities of ascorbic acid, which eliminated the possibility that the latter was being inactivated, for example by oxidation.

It is of interest to note in this connexion that the lowest value recorded in the present investigation, 15 micrograms per cent., was obtained from a patient with scurvy. On treatment with ascorbic acid the value rose steadily to 90 micrograms per cent. In 11 other male subjects whose plasma ascorbic acid level, determined as part of another investigation, was abnormally low, that is, less than 0·05 mg. per 100 c.c., but in whom there were no symptoms of scurvy, a mean value of $139 \pm 5{\cdot}8$ with standard deviation 19·4 was obtained, which was not significantly different from the control group. In the cases of pernicious anaemia mentioned above, serum-iron levels during treatment were observed to fall, levels as low as 30 micrograms per cent. being obtained shortly after the commencement of liver therapy.

Discussion

The serum-iron values obtained here for normal subjects need little comment. It is difficult to understand why the earlier results of Moore, Arrowsmith, Quilligan, and Read (1937) were consistently lower than those of

Vahlquist (1941) and those reported in the present paper. The lower values in women might possibly be explained by assuming that a high percentage of specimens was taken during menstruation. A reliable average would be obtained only from a group of subjects of whom one-sixth or one-fifth were menstruating at the time of assay, but it seems that this is not the explanation, since the values for normal men are also lower.

The absence of significantly raised values for serum-iron in the haemolytic anaemias may be explained on the assumption that in these cases iron was being removed from the serum for haemoglobin regeneration at approximately the same rate as haemoglobin breakdown was going on in the reticulo-endothelial cells. Since simultaneous storage of iron may also be taking place in these cells, raised serum-iron levels may be expected only during acute haemolytic crises, when the rate of haemoglobin breakdown is greater than that of iron utilization and iron storage by the reticulo-endothelial cells.

The role of ascorbic acid in promoting an increased rate of haemoglobin formation is difficult to assess. The absorption of iron may be said to depend on

(*a*) the need of the organism for iron

(*b*) the conversion and maintenance of iron in an absorbable (ferrous) form; gastric acidity appears to play an important part in this

(*c*) the permeability of the absorbing cells to iron.

Ascorbic acid given by mouth will certainly influence (*b*) and possibly (*c*) and may itself aid in haemoglobin synthesis. Thus Heilmeyer and Plötner (1936) have found that intravenous injection of ferrous ascorbate produces haemoglobin regeneration in excess of that calculated from the amount of iron injected; and Moore, Bredman, Minnich, and Arrowsmith (1940) have reported that injection of ascorbic acid causes marked lowering of the serum-iron level, which would point to a utilization of iron for haemoglobin synthesis. On the other hand, Croft and Snorf (1939) find no correlation between anaemia and low plasma vitamin C levels. It is likely, in the group of patients responding to small doses of iron together with large doses of vitamin C, that the latter is acting mainly in its capacity as a reducing agent, thus influencing factor (*b*). In the patient described as being resistant to intensive iron-vitamin C therapy, it may be suggested that factor (*c*) is at fault.

Determinations of serum-iron are of more value in the study of problems of nutrition and blood formation than in routine clinical work, but there are nevertheless certain ways in which they may be helpful in practice. They show whether iron is being absorbed, and in our experience resistance to treatment by iron in hypochromic anaemia is usually due to failure of absorption. A fall in serum-iron is one of the earliest indications of the response to effective therapy in pernicious anaemia. It is probable also that the high serum-iron in aplastic anaemia is of some differential diagnostic value.

Summary

1. Serum-iron values have been measured in a series of 70 normal controls and in patients with various types of anaemia.

2. Evidence has been obtained for a menstrual periodicity in the serum-iron of normal women.

3. The effectiveness of small doses of iron may be greatly increased by simultaneous administration of ascorbic acid.

4. Serum-iron in a small group of 'vitamin C deficient' male subjects did not differ from the normal values, but the level was much reduced in a patient with frank scurvy.

I wish to thank Professor L. J. Witts and Mr. J. R. P. O'Brien for their valuable advice and criticism. The main part of the work was carried out with the technical assistance of Miss Barbara Mallett.

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LOSS OF WEIGHT IN OBESE PATIENTS ON SUB-MAINTENANCE DIETS AND THE EFFECT OF VARIATION IN THE RATIO OF CARBOHYDRATE TO FAT IN THE DIET[1]

By A. B. ANDERSON

(From the Biochemical Laboratory, Department of Pathology of the University and Royal Infirmary, Glasgow)

The reduction of weight of obese subjects by dietary means has been the subject of numerous investigations, and extensive reviews have appeared recently (Rony, 1940; Newburgh, 1942). Little attention, however, has been paid to the effects of variations in the carbohydrate-fat ratio in reducing diets. Lyon and Dunlop (1932) reported that the loss in weight on 1,000 calorie diets appeared to be inversely proportional to the carbohydrate content of the food. Benedict and Carpenter (1910) found a similar effect in normal men performing work with a continuous loss of energy of 500 calories per diem. Further work on this subject is reported in the first part of the present paper. The second part deals with the quantitative relationship between the calorie deficit and the daily loss of weight in different subjects.

Methods

The subjects consisted of a number of obese patients who had been referred to the metabolic wards for investigation and treatment. All were in the wards under supervision for the duration of the investigation, but were not confined to bed. They were weighed on an accurate balance at the same time each day, to the nearest 0·1 kg. The basal metabolic rate was determined by the Douglas bag and Haldane apparatus. A Volhard water excretion test was carried out in the majority of patients. One litre of water was given on an empty stomach and the urine collected at half-hourly intervals for four hours. A total excretion of less than 800 c.c. was considered to indicate retention of water. After these and other preliminary investigations had been made, the dietary treatment was started. The diets were cooked and weighed in the ward kitchen, and the calorie values and composition were taken from the tables given by Sherman (1932). For analysis, complete half diets were dried, ground up, sampled, and analysed for nitrogen and chloride. The fat in the high-fat diets was removed before drying, and estimated separately.

[1] Received September 28, 1943.

Effect of Varying Proportions of Carbohydrate and Fat in the Diet

The experiments were started with the tentative hypothesis that the obese person had, to a large extent, ceased to oxidize fat, and that it might be possible to stimulate fat metabolism by feeding with diets of low calorie value, but of relatively high fat content. High-fat low-carbohydrate diets

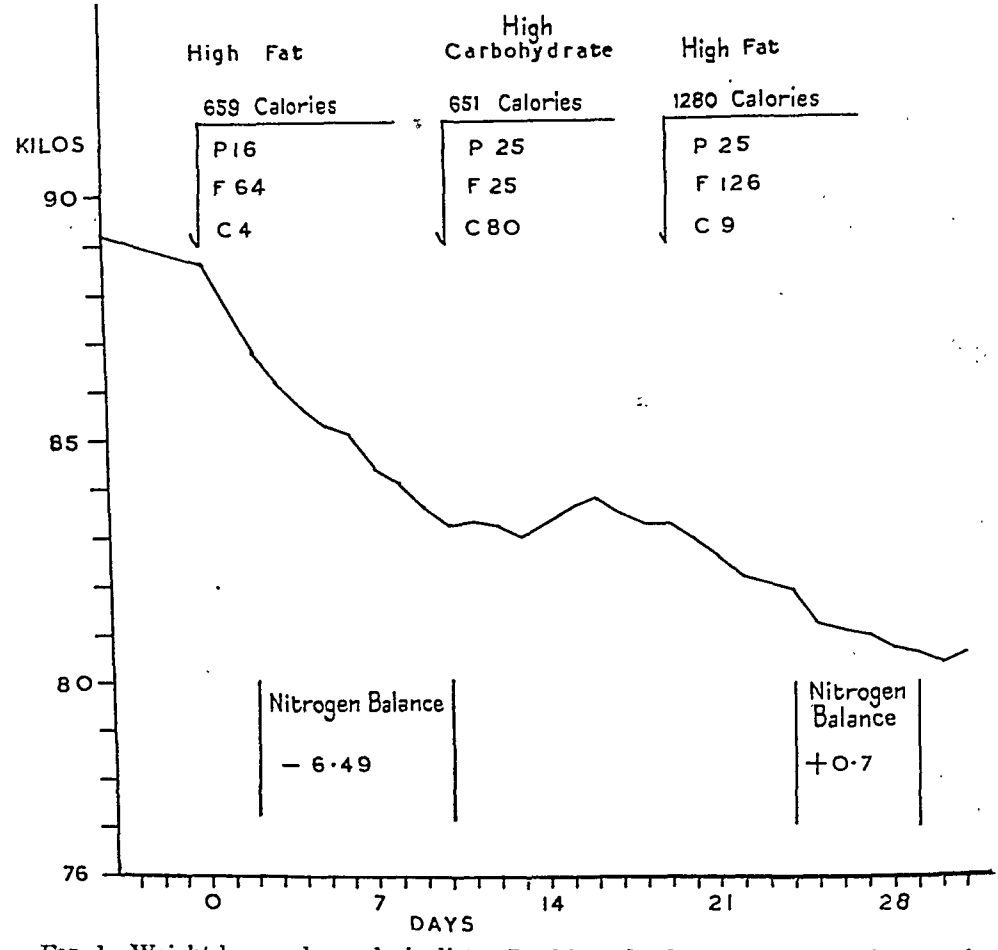

FIG. 1. Weight-loss on low calorie diets. In this and subsequent figures the protein, fat, and carbohydrate of the diets are given to the nearest gram.

and low-fat high-carbohydrate diets, of approximately the same protein and calorie value, were given in succession to the same patient. At first it appeared as if a greater fall in weight occurred on the high-fat diets than on the high-carbohydrate diets. This is illustrated by the two following cases.

Case 1. A single woman, aged 28 years, weight 89·2 kg., 65 per. cent. over ideal weight, basal metabolic rate − 23 per cent.

She had complained of increasing weight for the past two years and a pain in the right side for four years. Four years previously the menses had become irregular, lasting one day approximately every eight weeks. At the same time there was leucorrhoea. Dilatation and curettage of the uterus

was performed in another hospital a year before admission. Since then the menses had been regular and the leucorrhoea had ceased.

Examination revealed a large obese woman with some loss of hair from the top of the head. The skin was not noticeably dry. Blood-pressure was 135/90. Palpation of the abdomen revealed tenderness in the right iliac fossa. An X-ray of the skull showed a small sella turcica.

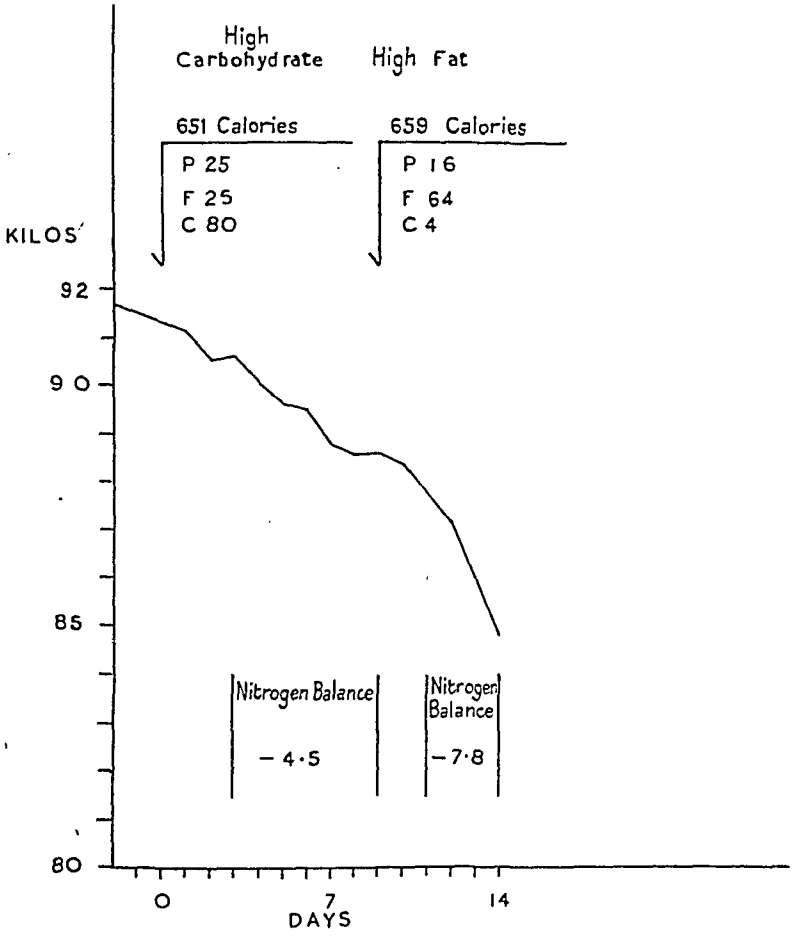

FIG. 2

This patient was given an high-fat diet of 659 calories, and Fig. 1 shows that on this diet there was a rapid fall in weight, averaging 500 gm. per diem for 10 days, with a negative nitrogen balance of 6 gm.; when the diet was changed to a 651 calorie high-carbohydrate diet, no loss of weight occurred over nine days, but on changing to a high-fat diet of 1,280 calories there was a steady loss of weight for 10 days, averaging 270 gm. per diem, with a slight positive nitrogen balance in the last five days.

Case 2. A married woman, aged 34 years, weight 91 kg., 70 per cent. over ideal weight.

The patient complained of gradually increasing weight since her marriage 10 years previously. There was no history of serious illness. She had had two children, and the menses were regular with normal loss.

On examination she was a healthy looking, obese woman; the hair was normal and the skin smooth and moist. General examination did not reveal anything abnormal, and the blood-pressure was 150/90.

In this case, as shown in Fig. 2, the 651 calorie high-carbohydrate diet was associated with a considerable loss of weight, but a much greater loss was

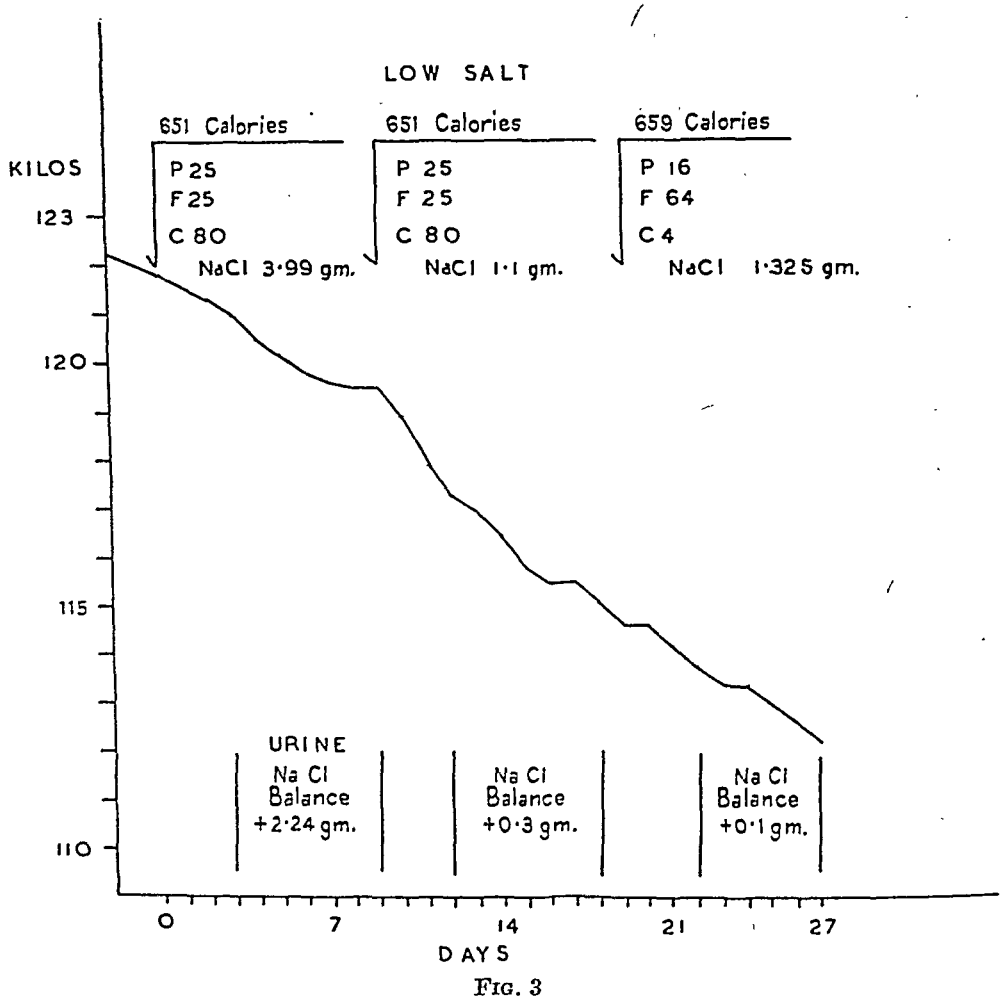

FIG. 3

obtained on the 659 calorie high-fat diet. The nitrogen balance was negative on both diets. An analysis of these two diets showed that, besides the difference in the quantity of carbohydrate and fat, the diets also differed in salt content. The chloride content of the high-carbohydrate diet was found to be 3·99 gm. per cent. as sodium chloride, while that of the high-fat diet was 1·33 gm. per cent. If the salt content of the high-carbohydrate diet was reduced to 1·1 gm. per cent. the loss of weight was equal to that obtained with the high-fat diet.

Case 3. A married woman, aged 44 years, weight 122 kg.

She complained of obesity, shortness of breath, and headaches. Two years previously she had become much stouter, and had found difficulty in walking

because of shortness of breath. She had had enteric fever 11 years previously. There were nine children, and the menses were regular and normal.

On examination she was an extremely obese woman, breathless, and with cyanosis of the lips. The heart size could not be determined on account of the obesity. There were no adventitious sounds. The pulse-rate was 84 and the blood-pressure 140/90. No other abnormalities were detected.

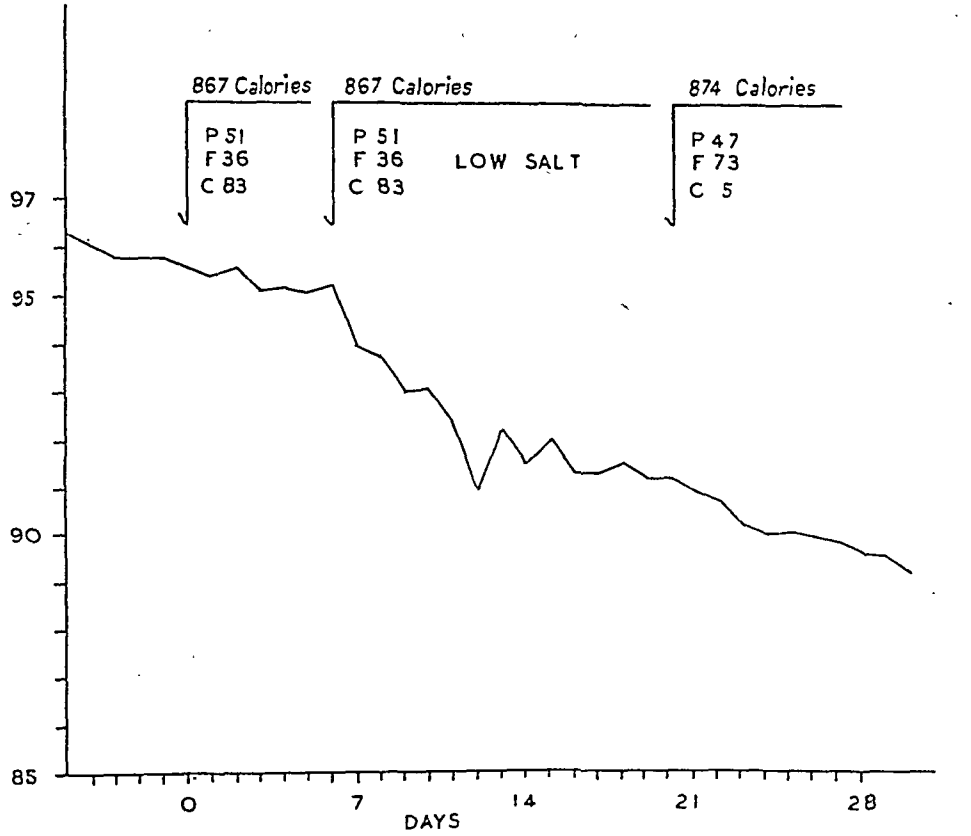

FIG. 4

Fig. 3 shows that there was a slow loss of weight on the ordinary high-carbohydrate diet of 651 calories, with a retention of 2·24 gm. of sodium chloride per diem, while on the low-salt diet a much more rapid loss occurred, and the patient was practically in chloride balance. On changing to the high-fat diet the weight-loss continued at the same rate and she remained in chloride balance. This effect of reducing the salt content is better illustrated by Case 4.

Case 4. A single woman aged 31 years, weight 96·3 kg., 65 per cent. over ideal weight, basal metabolic rate +1 per cent.

She complained of obesity and pain in the right side. Since the patient started to menstruate at the age of 18 years she had been gradually putting on weight, but during the three months previous to admission the gain in weight had been excessive. No history of serious illness was obtained. The menses were irregular with scanty loss, and five months previously there had been amenorrhoea for three months.

On examination she was an obese woman, the hair normal, and the skin soft. The blood-pressure was 115/75. There was tenderness to deep pressure in the right iliac fossa. No other abnormalities were found. She complained of a gnawing pain in the abdomen in the region of tenderness, but there had not been any nausea or vomiting.

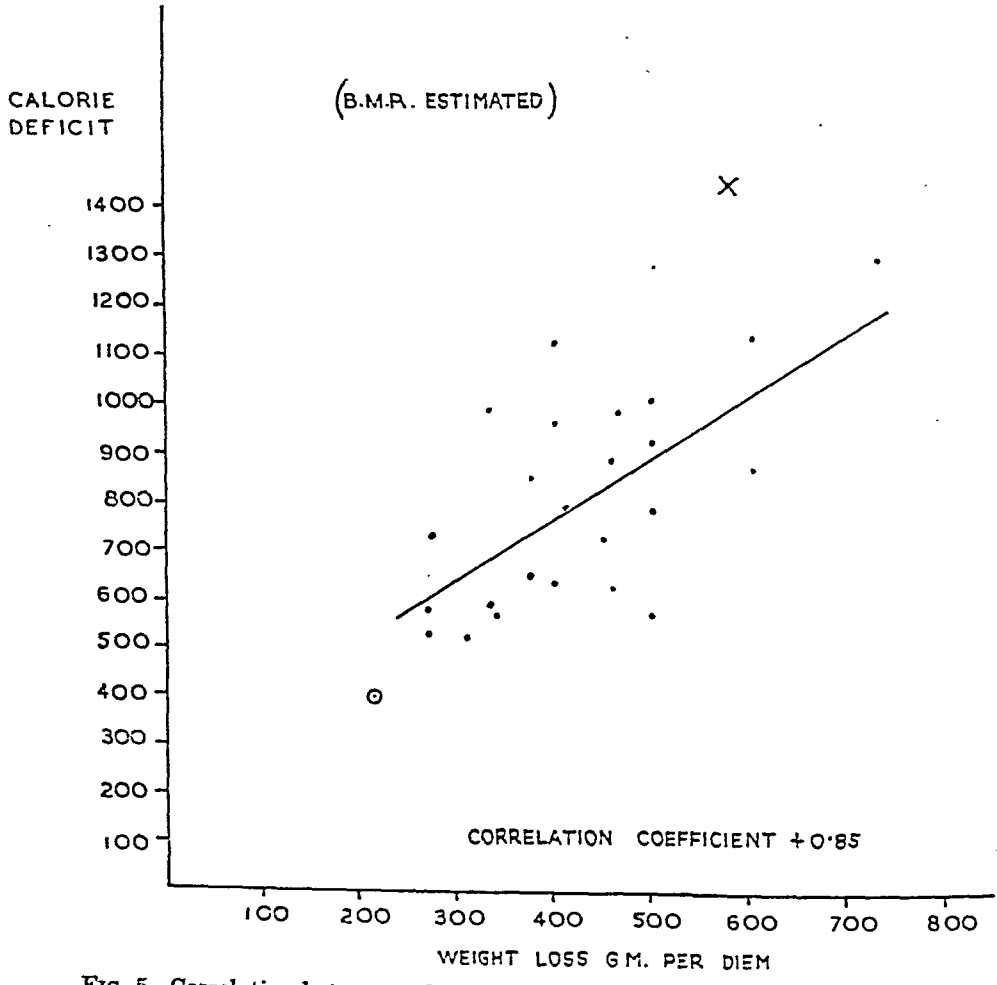

FIG. 5. Correlation between calorie deficit and average daily loss of weight
Equation for the line is calorie deficit = 1·25 × weight-loss + 272.
X represents Benedict's fasting man for first 10 days.
⊙ the average for Benedict's squad of young men on sub-maintenance diet.

In this patient there was hardly any loss of weight for a week on an ordinary high-carbohydrate diet of 867 calories, but on changing to a low-salt diet of the same composition, there was a rapid initial loss of weight, followed by a steady loss which was not increased by changing to the high-fat diet (Fig. 4). The protein content of 50 gm. in these 867 calorie diets is at a more satisfactory level than that in the 651 calorie diets. Several cases not shown here were found to be in nitrogen balance while losing weight on these diets. The low-salt high-carbohydrate diet has been given to a number of patients with results which are described below.

Relation between Calorie Deficit and Loss in Weight

The purpose of this part of the investigation was to determine the relationship between calorie deficit and weight-loss in different obese subjects. The material for the study consisted of 22 patients, one male, and the rest female, of ages from 14 to 56 years. The excess weight over the ideal weight varied

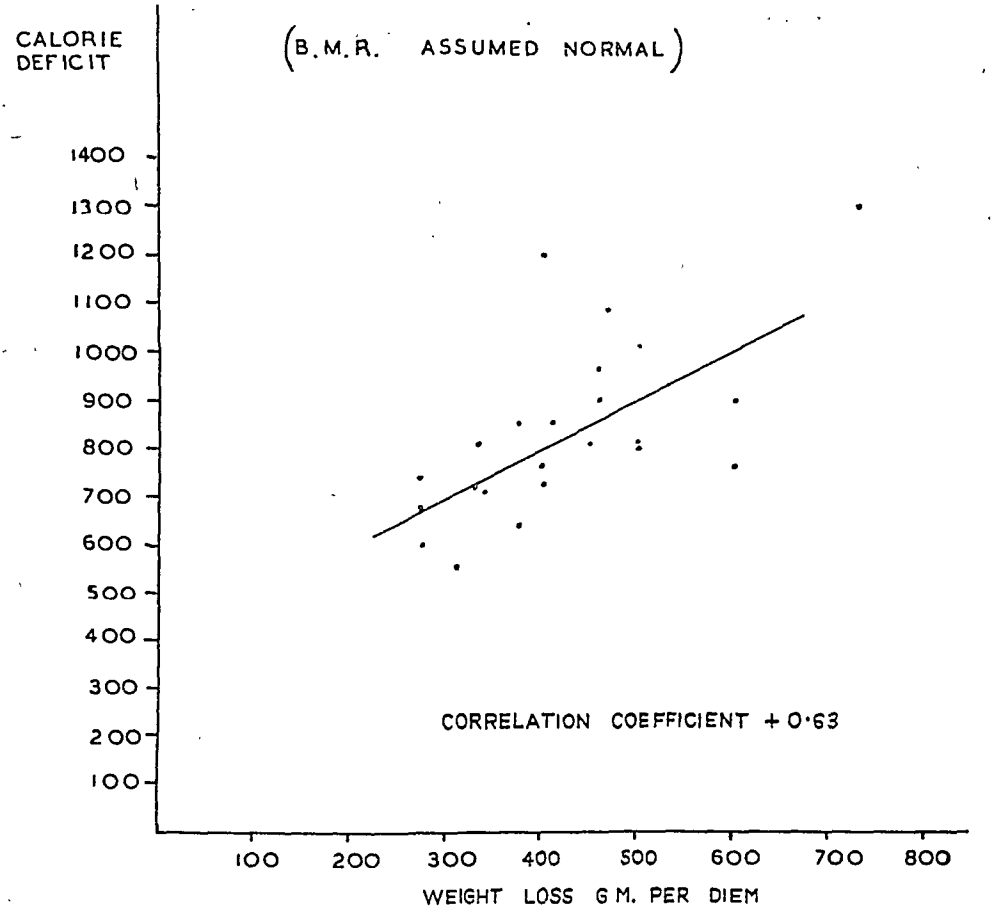

FIG. 6

from 24 to 148 per cent. with a mean of 75 per cent. Various clinical 'types' of obesity were represented, and, without entering into a discussion of the much debated question of the influence of endocrine factors in obesity, it will suffice to record that of the 21 female patients, four had amenorrhoea and five showed gross menstrual irregularity. The basal metabolic rate was within ± 15 per cent. of the average normal with the exception of three cases, one of -16 per cent., one of -19 per cent., and one of $+16$ per cent. The water excretion test was performed in 20 of the patients, and seven showed a definite retention of water. These findings are tabulated in the Appendix, Cases 4 to 25.

The same diet was given to all, namely, a low-salt diet of 867 calories, composed of protein 50 gm., fat 36 gm., carbohydrate 83 gm. All patients

lost weight steadily on this diet. The average daily loss for the first 7 to 10 days was plotted against the minimum calorie deficit, a figure determined by subtracting the 867 calories supplied by the diet from the basal requirement of each patient for 24 hours taken from the basal metabolic rate found. It must be noted that the calorie deficit represents only the basal deficit; no allowance is made for the calories required for sitting up, standing, or other activities, which varied considerably with the individual, and were not measured.

The scatter diagram obtained by plotting these results is shown in Fig. 5. For comparison, the loss of weight reported by Benedict (1915) for a starving man during the first 10 days of fasting is plotted against his basal metabolism at the beginning of the fast, and marked by a cross in Fig. 5. Another figure for comparison is taken from Benedict, Miles, Roth, and Smith's (1919) work on a group of healthy young men on a sub-maintenance diet. The average figure for squad B, using the rearrangement of Benedict's figures given by Lusk (1928), is shown as a circle in Fig. 5. It will be seen that there is a close correlation between the weight-loss and the calorie deficit, the coefficient of correlation being $+0{\cdot}85$. The equation for the line is calorie deficit $= 1{\cdot}25 \times$ weight-loss $+ 272$. The average for Benedict's squad of young men is of much the same order, while the fasting man lost relatively less weight. The calorie deficits were then recalculated, assuming the basal metabolism of each patient to be the average normal and calculating the requirement from Boothby and Sandiford's (1929) modification of the Dubois standards. These figures were plotted against the actual weight-losses and the scatter diagram obtained is shown in Fig. 6. It will be seen that the correlation is much less close, the coefficient being only $+0{\cdot}63$.

Discussion

From the results given in the first section, it is clear that the finding by previous workers that, with diets of the same calorific value, the low carbohydrate diets produced the greatest loss of weight, can be explained by a higher salt content in the high-carbohydrate diets. The failure to lose weight rapidly on a high-carbohydrate diet of ordinary salt content is probably due to retention of water and salt in the tissues. Water and salt retention in the obese is a well recognized phenomenon, and has been studied extensively by Newburgh and Johnston (1930), who showed that obese patients, despite a large calorie deficit, might not lose any weight for as long as nine days, and then undergo a rapid loss to the expected level. Newburgh and Johnston found that departures from the predicted weight were always accounted for by storage or loss of water.

That many obese patients show a retention of water in the Volhard water excretion test has been reported by Zondek (1925) and Wohl and Ettelson (1935); the latter, in a series of 36 overweight patients, found 19 with some degree of water retention. Rowntree and Brunsting (1933) have described two obese patients with extreme water retention, in whom simple dehydration produced by the administration of ammonium salts and mercurial diuretics was followed by a reduction in weight to practically a normal level.

Water retention on diets of normal salt content is of practical importance in the treatment of obesity, as patients tend to become discouraged if dieting is not followed by obvious loss of weight. That a normal man who is being underfed may show a similar retention of water to that occurring in the obese has been found by a careful study of the water balance by Wiley and Newburgh (1931).

In considering calorie deficit and weight-loss, it must be remarked that the relationship found in the observations described here holds only for the region covered by the observations, namely a calorie deficit of 500 to 1,300 calories. It is not justifiable to extend the line outside these limits; this would, for example, give no loss of weight with a calorie deficit standing at 273. It can be concluded from the close correlation found within these limits that the various 'types' of obese patient react in the same way to undernutrition, and that, provided a low-salt diet is being taken, the weight-loss can be approximately predicted.

Summary

(1) In obese subjects on low calorie diets, the greater weight-loss on high-fat diets as compared with that on high-carbohydrate diets of equal calorific value was due to the higher salt content of the high-carbohydrate diets, leading to retention of water and salt.

(2) When the salt content of the high-carbohydrate diet was reduced to that of the high-fat diet, the loss of weight was the same on both diets.

(3) In 24 patients of various clinical 'types' of obesity, all on the same low-salt diet of 867 calories, a close correlation was found between the loss of weight and the calorie deficit, obtained by subtracting the calories supplied by the diet from the daily basal requirement found by determination of the basal metabolism.

This investigation was carried out partly during the tenure of a Carnegie Teaching Fellowship in the University of Glasgow. I am much indebted to my medical and surgical colleagues who have referred cases of obesity to me, and also to the Sisters and the Nursing Staff of the metabolic wards for their care in preparation of the diets and supervision of the patients. Part of the expenses of the work were defrayed from a grant from the Rankin Fund of the University of Glasgow.

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APPENDIX

Summary of Cases

Case No.	Age	Civil state	No. of children	Menstrual history	Weight kg.	Percentage over ideal weight	B.M.R. %	Excretion of water	B.-P.	Onset of obesity
1	28	S.	—	Irregular, 1/60	89	65	−23	—	135/90	2 years previously
2	34	M.	2	Regular. Normal loss	91	70	—	—	150/90	Gradual increase since marriage
3	44	M.	9	Regular. Normal loss	122	—	—	—	140/90	2 years
4	31	S.	—	Irregular. Scanty loss	96	65	+1	—	115/75	Gradual since puberty at 18
5	40	Male	—	—	87	30	±0	—	—	3 years previously
6	29	M.	0	Amenorrhoea, 5 months	122	100	−4	1,440	132/80	5 months, rapidly
7	42	M.	10	Regular, 3/30. Normal loss	108	100	−3	387	140/70	Gradually over period of years
8	29	M.	0	Regular, 1/28. Scanty loss	66	24	−2	983	—	Only very slight obesity
9	23	S.	—	Amenorrhoea, 5 years	84	38	+7	735	120/70	5 years, gradually
10	21	M.	0	Amenorrhoea, 2 years	79	42	−9	1,110	115/90	2 years, 1 year after marriage
11	14	S.	—	Regular. Puberty at 12	83	43	−19	1,131	—	2 years
12	26	S.	—	Regular. Normal loss. Puberty at 13	95	82	−5	498	140/90	2 years
13	29	M.	0	Normal loss, 4/21 to 28	137	117	−3	950	140/100	Gradually. From marriage 6 years before
14	36	M.	5	Regular. Slight loss	109	101	−5	1,030	175/110	From first pregnancy 12 years previously
15	31	M.	1	Infrequent, 6 to 12 weeks	100	85	+6	930	145/110	7 years. Since marriage
16	41	M.	3	Regular. Normal loss	134	148	+13	1,065	120/90	8 years, after third child
17	15	S.	—	Regular. Puberty at 9	137	132	−1	890	140/88	Obese since birth. Birth-weight 14 lb.
18	57	M.	—	Menopause	85	47	−9	715	—	—
19	47	W.	2	Regular. Normal loss	140	134	+13	195	150/95	Always stout, gradually worse after marriage
20	56	M.	12	Menopause, 5 years	109	110	+16	740	175/120	Gradual since marriage 36 years previously
21	27	M.	2	Irregular. 3/3 to 6 months. Scanty loss	94	62	−16	1,385	125/85	8 years. After first pregnancy with puerperal sepsis
22	47	M.	9	Regular. Normal loss	96	69	+13	1,420	155/95	Gradual since birth of first child. 28 years
23	27	M.	0	Amenorrhoea, 2 years	70	28	+8	1,270	140/95	2 years, since marriage
24	17	S.	—	Regular. Normal loss	71	32	+14	790	136/84	5 years
25	43	W.	—	Regular. Normal loss	106	86	−1	730	157/95	1 year, rapid gain

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'FIBROSITIS' OF THE BACK[1]

By W. S. C. COPEMAN and W. L. ACKERMAN

With Plate 2

The authors believe that the ground covered by this study has not previously been systematically explored. The work has been carried out during active service in an area in which the impossibility of access to medical literature explains the lack of references to any relevant papers.

The frequency of 'fibrositis' of the back seen amongst otherwise healthy young men in the Army stimulated our interest in this condition. As a first step, exact measurements were taken of the site of the painful focus in a large number of sufferers and a 'pain chart' was plotted. The back of every patient who died in hospital from any cause was then systematically examined, with special reference to these areas.

As a result of this, and of subsequent clinical observations and biopsies, conclusions have been arrived at which seem to explain certain cases of 'fibrositis' of the back and, it is believed, elsewhere.

The Nature of the Pain

Fibrositic pain in the back is a well-recognized clinical entity, although its aetiology has always been a matter for speculation. Comroe (1942) in the latest edition of *Arthritis and Allied Conditions* states that its aetiology is unknown and that there are no specific pathological lesions.

It is only comparatively recently that Kellgren and others have pointed out that the pain generally has its origin in certain focal points, from which the more generalized subjective pain complained of by the patient is referred according to a segmental plan. This referred pain may be at a considerable distance from its real origin, as exemplified in many cases of sciatica, the original focal point of which may be found in the lumbar or gluteal muscles. These points, which go by various names—trigger points, tender rheumatic nodules, myalgic spots—are definite clinical entities in so far that when they are found by the palpating finger the patient winces involuntarily. Pressure of the same intensity exerted only a few millimetres away will not produce the same response, although a certain degree of more generalized muscle tenderness may be present. Pain which is referred to other areas from such a point will also generally be reproduced by this pressure. The treatment of these points by the injection of local anaesthetics in saline is, as is now well known, usually successful provided that the injection is made with great exactitude into the centre of the point, not always an easy procedure.

[1] Received January 19, 1944.

It has recently been observed by one of us (W.S.C.C.) that the pain in the back which accompanies most of the pyrexial illnesses, such as influenza, the exanthemata, malaria, dysentery, and infective hepatitis, is of the same nature and pattern. It was shown, moreover, that although the pain passes off at the end of the pyrexia the trigger point will persist unknown to the patient in a proportion of cases. It is thought that this constitutes the basis for fibrositis at a later date in such patients, when further infections or injuries occur to reactivate the condition. As will be shown, these trigger points tend to occur in certain predictable sites in the lumbar and gluteal areas, and also throughout most of the dorsal area (see Fig. 1). It was found, however, in studying tender spots which occurred within an area extending for about two inches on each side of the spinal column in the dorsal area, that these, unlike those referred to elsewhere, did not appear to occur in fixed positions. It was also remarked that there were certain clinical differences between the pain arising within this area and that occurring elsewhere in the back. Firstly, it is much rarer for pain from these spots to be referred to a distance; and the pain seems to be produced by the contraction of specific muscle groups. Secondly, the onset of pain in this situation is preceded by localized stiffness of gradual onset, in contrast to the rapid onset of pain in other areas. Finally, if the trigger point be carefully palpated, preferably after massage, it can be defined as an especially tender point along the course of an elongated fibrous structure, which can be rolled beneath the finger. At certain phases, if deep pressure be maintained over the spot and the patient be made to move, distinct crepitus can be felt, such as occurs with tenosynovitis elsewhere. It was therefore inferred that pain occurring within this limited area in the dorsal region is due to a tenosynovitis of the terminal tendons. This inference receives confirmation from dissection of this area, as will be shown below.

The Sites of the Pain

Measurements have been taken in a large number of patients suffering from chronic fibrositis and from the more transient pains occurring during other illnesses, and clearly show that, with the exception discussed above, certain situations are chiefly favoured by the tender spots. The aggregate of these sites is plotted in Figs. 1 and 2, from 50 unselected cases.

In the dorsal region (Fig. 1) the most constant point of tenderness is found over the supraspinatus tendon, just before it passes deep to the acromial process of the scapula. In the interscapular region tender spots may occur anywhere in the vertical plane within 2½ in. of the mid-line, which represents the width of the sacrospinalis muscles at this level. Another more constant site is along the medial border of the scapula from the level of its spine downwards. A small area where the lower costal margin crosses the line of the outer edge of the sacrospinalis muscle is also a common site for pain.

In the lumbar region (Fig. 2) the most common sites are at the edge of the sacrospinalis muscle just above the iliac crest, one inch above this level, and at the level at which the latissimus dorsi crosses the sacrospinalis. In the gluteal region (Fig. 2) points may be found all along the crest of the ilium and for a distance of about two inches below it. They may also be found

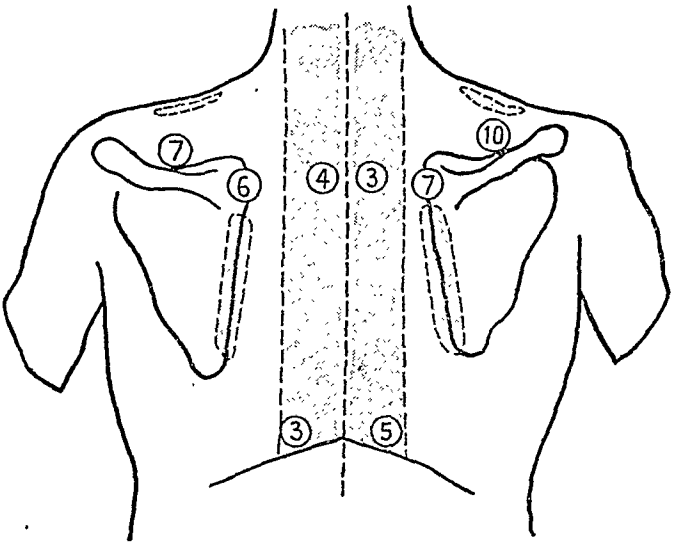

FIG. 1. *The shaded area covers the location of the 'trigger points' in 25 consecutive* cases of fibrositis. (Where a significant number of points coincided, the number of these is indicated in the circles.)

along the sacro-iliac junction, where the deep fascia is attached. They are not commonly found elsewhere in the buttock.

Dissection of the Normal Back

Fourteen backs were dissected and special attention was paid to those areas marked in Figs. 1 and 2 as being the commonest sites of fibrositis. After one or two dissections our preconceived ideas of the importance of the fibrous tissue became modified, as no fibrous lesions, abnormalities, or adhesions were found at a deeper level than the subcutaneous tissues; and moreover it became obvious that the basic fat pattern, which persisted in even the most cachectic bodies, corresponded exactly with the pain pattern of Figs. 1 and 2. Increasing attention was therefore paid in subsequent dissections to the relationships of this fat and the fibrous tissues.

In text-books of anatomy not much information can be gained regarding the relationship of the fascial layers of the back with the body fat. The following simplified description seems to be justified. Deep to the subcutaneous fat and areolar tissue lies the highly vascular superficial fascia, which forms a continuous sheet from the neck to the gluteal region. For the most part the space between this and the deep fascia is a potential one, containing little or no fat. In certain well-defined places, however, deposits

of pinkish fat constantly occur. It is these, together with the equally constant deep areas to be described, which constitute what we have called the basic fat pattern. In these situations fat was still present even in the most grossly wasted bodies in which most of the fat elsewhere had disappeared (four of the bodies examined were of patients who had been in coma for

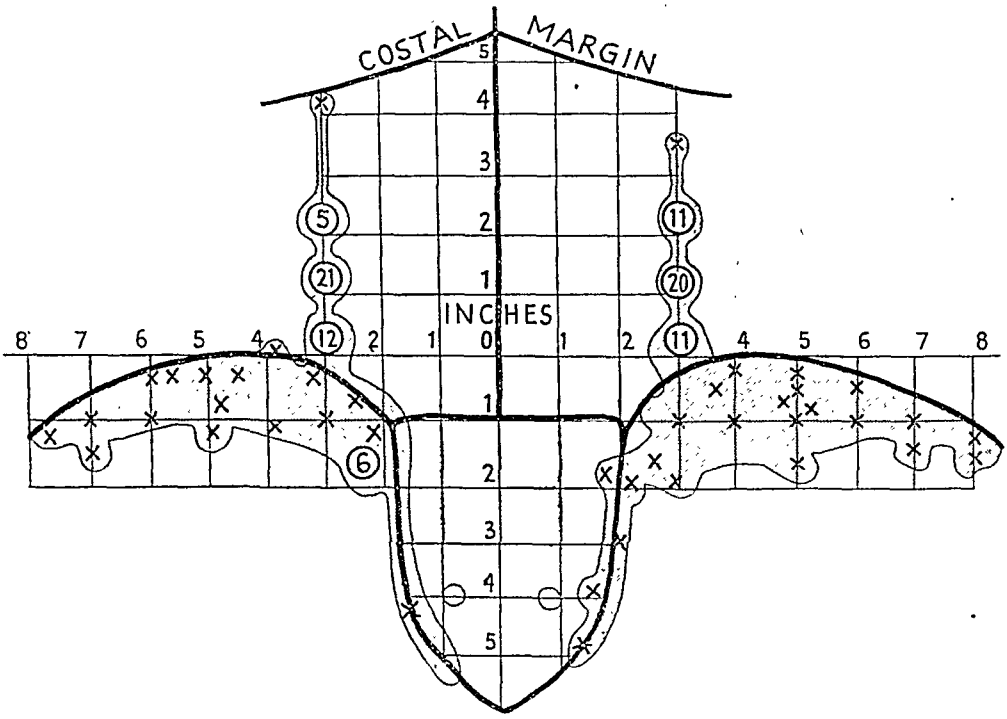

FIG. 2. The shaded area shows the location of the 'trigger points' in 50 consecutive cases of fibrositis.

several days prior to death and were extremely emaciated). In obese persons this fat pattern tends to be obscured by the more generalized deposition of fat. The distribution of this basic fat is shown in Fig. 3. It was noticed that the fasciae were not of uniform thickness, being notably thinner in certain places, whilst not infrequently actual deficiencies in the membranes were found. In these places the underlying fat tended to bulge through, sometimes resulting in a complete herniation (fat hernia).

The basic fat pattern. The basic fat pattern can best be described in separate parts as it occurs in the dorsal region, the lumbar region, and the gluteal region.

In the dorsal region it is found lying along the tendon of the supraspinatus muscle running outwards towards the shoulder, where it becomes incorporated into the synovial sheath of the tendon and continuous with that of the deltoid bursa. In two oedematous bodies oedema of this fat appeared to have caused some constriction of the tendon at the point where it passes deep to the acromial process.

It is found deep to the investing fascia of the trapezius muscle, outlining its borders. A similar appearance is found at the medial border of the scapula, from the root of the spine downwards. In two subjects small flattened herniations of this fat through the fascia were found, and in a third pressure applied near an obviously weak spot in the membrane produced herniation.

It is also found in the synovial sheaths, when these occur, of tendinous portions of the sacrospinalis muscles. It seemed that these tendinous portions were more commonly present in subjects with a long thin type of back than in those of a more stocky build. The explanation of this may lie in Harris's suggestion that a tendon sheath is developed where it is required and makes its appearance in response to the range of movement, which is obviously greater in the former type of back. The possibility that fibrositic pain experienced within the area of this muscle group may be due to a synovitis of these tendon sheaths, and not to the alternative mechanisms which it is thought are causative elsewhere, has already been mentioned. The pain which is so commonly found over the supraspinatous tendon may be due to a similar cause.

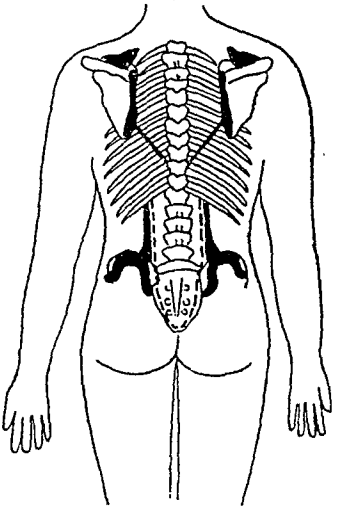

FIG. 3. The 'basic fat pattern'. This appears to represent the irreducible minimum of fat in the back. The dotted lines represent the deeper portion contained in the fascial angle along the outer edge of the sacrospinalis muscle.

Detailed examination of the synovial sheaths of all the tendons and joints which were examined showed that they consisted largely of rather fibrous fat, which forms a loose tunnel through which the tendon moves. As the tendons are themselves avascular and their microscopic structure does not suggest that they can readily become oedematous owing to the dense nature of their constituent fibrous tissue, it is suggested that it is this investing fatty capsule which becomes oedematous, thus narrowing the lumen of the tendon sheath and impeding its action, causing stiffness. This may ultimately lead to the cessation of voluntary movement on account of pain. This hypothesis of the causation of tenosynovitis is supported clinically by the sequence of onset of nontraumatic synovitis in any joint, which starts generally with a period of stiffness and tightness which precedes definite pain by some hours, this sequence suggesting a gradually increasing compression of the tendon, so impeding its free movement. If this process continues, and there is a joint cavity in anatomical relationship with the affected sheath, a secondary joint effusion will also occur. In the back this cannot happen, as there is no joint in relationship with the tendons of the sacrospinalis. Other clinical observations which support this hypothesis have already been discussed.

Another place where painful spots are commonly situated in the dorsal area is around the junction of the lower costal margin and the outer border of the sacrospinalis muscles. Dissection reveals the presence of two or three fibrous bands, which cross the sacrospinalis at this region, constricting it where they do so. Those presumably represent a common variant of the serratus minor posterior muscle (which Gray's *Anatomy* describes as being a muscular structure). In cases in which synovial fat was seen lying beneath, it seemed to be under considerable tension, bulging out when this muscle was divided.

In the lumbar region, the sacrospinalis muscle is edged with fat, some lying superficial to the deep fascia (lumbar fat pad) and some lying within the angle made by the deep fascia as it splits to invest this muscle. In very wasted bodies this fat is deficient along the upper portion, where it lies under cover of the latissimus dorsi muscle. Below this strip the fat follows the line of attachment of the deep fascia and the muscle along the sacro-iliac junction. Small fat herniae have frequently been observed in both these areas.

It was found when the measurements were being taken for Fig. 1 that although a majority of the trigger points plotted occurred at certain levels these varied by about $\frac{1}{2}$ in. on their horizontal plane. Dissection showed that this was due to variation in the width of the sacrospinalis muscle in accordance with the muscular development of the subject. These variations in the horizontal plane have not therefore been illustrated. In the vertical plane, the levels at which the trigger points cluster most thickly are at the junction of the outer border of the erector spinae with the iliac crest, one to one and a half inches above the crest, and two to two and a half inches above the crest.

Careful dissection at these areas, through the basic fat pad which lies in the superficial fascia, revealed that it was at these points that the cutaneous branches of the posterior primary rami of the first three lumbar nerves pierced the deep fascia, after leaving the body of the muscle. This they do through definite foramina accompanied by small blood-vessels. In two of the bodies a small tuft of fat lobules was protruding through the foramen, probably as the result of post-mortem pressure. There is a small horizontal fold of the membrane, overhanging each foramen, which probably acts as a valve and prevents herniation of fat when the back is flexed. As the result of the investigations recorded in the next section it is believed that these valves do not always perform this function efficiently, and failure to do so allows herniation to occur; this may result in lumbago.

Apart from the lesions described above, it is not uncommon to find at intervals along the edge of the muscle small bubbles of deep fascia, containing a few lobules of fat bulging up from the angle in which it is contained. Firm pressure applied immediately adjacent to one of these potential herniae can easily convert it into a true fat hernia of the size of a pea or larger. These small herniae tend to occur at points where the fascia is

weaker, and give rise to no symptoms until some incident, such as sudden trauma or some pyrexial illness, which entails lying on the back for several days, produces an increase in the fat pressure and a painful degree of distension. This leads to oedema, which may perpetuate the condition.

In the gluteal region there is a crescent of pink fat, which extends along the crest of the ilium and for a distance of about two inches below. It is contained within the superficial fascia, and extends from the anterior superior spine back to the sacro-iliac junction, often sending a narrow prolongation down this area, as shown in Fig. 3. The dotted line indicates the similar tongue of fat which lies in this region, but at a deeper level, being contained in the angle of the deep fascia. It is thus continuous with the fat described along the edge of the sacrospinalis muscle in the lumbar region.

The fat along the iliac crest lies in layers, where it has split the superficial fascia in which it is contained, and it is common for the lobules of one layer to herniate into a more superficial layer, or laterally into an adjoining compartment, where the fibrous walls are weak or deficient. The fact that this pad of fat lies almost directly over the unyielding bone of the ilium may account for the common occurrence of such lesions in this area.

Fat Herniation

From what has been said it will be seen that fibrositic pain appears to have a topographical relationship to the basic fat pattern. Herniation of fat lobules through fascial weaknesses, deficiencies, or foramina was found not infrequently in the course of dissection, and, as will be shown later, these herniations can be the site of 'fibrositic' pain in the living patient. They can be subdivided into three types: the non-pedunculated, the pedunculated, and the foraminal.

In the *non-pedunculated type* of fat hernia, fat which lies under a fascial covering, as for instance in the angle of the deep fascia where it splits to invest the sacrospinalis muscle, or along the crest of the ilium, is always under tension and so will bulge into any potential hernial space which may be present, either as the result of congenital weakness or as the result of trauma. This tendency will be increased by muscular action. It is found at dissection that such potential herniae are not rare and should probably not be considered as being pathological unless they cause congestion and pain by constriction of the enclosed fat. In this case oedema or haemorrhage may have occurred, which by increasing the tension initiate a vicious circle, and so in time tend to make the condition chronic. In microscopic sections from biopsy specimens some degree of commencing fibrosis has also been seen, suggesting that if such a hernia were subjected to chronic 'strangulation' for a sufficiently long period, it might be converted into a true fibrous nodule. In no case so far met with has this occurred, although in one the history dated back 15 years. In the cadaver it is possible to increase the size of these potential herniae by applying pressure with the finger on either side.

and it is easy to visualize the possibility of this occurring in the body during life as the result of trauma or sudden muscular action.

Non-pedunculated herniae are most commonly found in the lumbar fat pad, which lies within the superficial fascia, and in its extension downwards which lies along the crest of the ilium, in the gluteal region. These tense swollen fat nodules can be palpated where they are sufficiently superficial, and when a nodule disappears as the result of heat and massage it seems reasonable to suppose that it has been composed of fat rather than fibrous tissue. A variant of this type of hernia is that which protrudes in a horizontal direction, the contents of one fibrous compartment herniating through an imperfection in the wall of the neighbouring compartment as the result of some extra tension (Case 3). This type occurs most frequently along the iliac crest, where the fat lies between the unyielding bone of the ilium and the thickest portion of the gluteal fascia.

The pedunculated type of hernia.[2] This type has not been found in the normal back, but has been found and removed in several patients who were operated upon (Cases 5 and 6). In each of these cases the onset of the pain was produced by a sudden strain several years previously. It is thought therefore that it is probably a late result of strangulation in a hernia originally of the non-pedunculated type. The appearance is similar to that of an ordinary pedunculated polyp, but a lobule of fat takes the place of the terminal polypoid tissue. This polyp lies in a layer of fat more superficial than that from which it springs, being connected with its roots by a pedicle which generally contains fibrous tissue and a blood-vessel. The pedicle sometimes appears to be twisted. Histologically there is generally some fibrous tissue merging into the terminal fat of the lobule, but no completely fibrous nodule has been met with at a deeper level than the subcutaneous tissue.

The foraminal type of hernia. This type was found only along the edges of the sacrospinalis muscles. These muscles are supplied by the lumbar nerves, in the first, second, and third of which the lateral branches of the posterior primary rami become cutaneous and pierce the deep fascia at the spots where the trigger points of fibrositic pain chiefly occur. These areas were exposed in all the cadavers and it was found that the nerves passed out in company with a small artery and vein through a foramen in the deep fascia of the muscle. Overhanging this was a narrow lateral fold of the fascia, so arranged as to occlude the foramen on flexion of the back. In several cases it was seen that this mechanism had apparently proved ineffective and a small tuft of fat lobules had also herniated through the foramen. In the cadaver it was sometimes possible to produce a herniation

[2] This type of fat hernia occurs not infrequently in the epigastric region. In 200 consecutive gastric cases examined by one of us five were found and removed. In three of these a pedicle was piercing the abdominal fascia and was continuous with the intra-abdominal fat. In the remaining two there appeared to be no intra-abdominal connexion. In all but one of these cases removal resulted in disappearance of the apparent gastric symptoms.

of this sort by direct pressure. In several cases (Nos. 9 and 10, for example) a herniation of this type was found to be the cause of sudden lumbago, and removal of the oedematous fat and enlargement of the foramen proved curative (Plate 2, Fig. 6). Although this type of herniation might theoretically occur in any of the nerve foramina, it has been proved to do so only in the case of the second and third lumbar nerves, whose foramina are not overlapped by the latissimus dorsi muscle. They were not overlapped in any of the 14 bodies dissected, although reference to Gray's *Anatomy* would suggest that they generally are so. The tone of this muscle probably proves sufficient to prevent a degree of fat herniation occurring enough to produce symptoms.

Foraminal herniation has not been found in the dorsal region, although if fat were present there is no reason why it should not occur in the case of the medial branches of the posterior primary rami of the upper six thoracic nerves which pierce the rhomboid and trapezius muscles.

Clinical Observations

Ten case histories will be given in full. These cases not only illustrate the clinical application of the anatomical observations recorded above, but afford therapeutic confirmation of our hypothesis regarding the origin of fibrositis in these cases, since in each instance the biopsy proved curative. A local injection of one per cent. procaine into the skin was the only anaesthetic employed.

Cases 1, 2, and 3 are examples of the non-pedunculated type of fat hernia. In Case 4 this condition was multiple; Cases 5 and 6 represented the pedunculated type, whilst 7 and 8 were of the bubble type of non-pedunculated hernia. Cases 9 and 10 were of the foraminal type.

Non-pedunculated Type

Case 1. Aged 21 years. (The simple type of hernia.)

Rheumatic fever when aged 11 years (in bed six weeks). Relapse when aged 14 years which followed scarlet fever (in bed five weeks). No recurrence and no rheumatic pains since then. No other illnesses. Six months before he was accidentally hit on the head with an iron bar and was admitted with sciatic pains and weakness in legs and back. He was in bed four weeks (developed tonsillitis after two weeks). After this he got up, but pain relapsed immediately. There was generalized tenderness over the muscles of the lower limbs and bilateral, very tender nodules 2½ in. from midline and 1½ in. below iliac crests. Pressure on the right caused a referred pain in the thigh, which radiated to the back of the knee. White cell count and differential count normal. Blood sedimentation rate 4 mm. in 1 hour.

The tender nodule in the right buttock was explored, after transfixing it with a needle. A large lobule of fat bulged into the wound as soon as the covering fascia was incised, and pressure on this caused pain of the type of which he had previously complained, as well as the referred pain down the thigh. The lobule was seen to have a blood-vessel running into it through

the deep fascia, but no pedicle. This nodule was removed, the pain disappeared, and there was no sign of recurrence when seen two months later.

Case 2. Aged 38 years. (The lateral type of hernia.)

He had suffered for several years with vague 'fibrositic' pains much affected by weather. These had become worse in past few years, and he had gained weight in spite of moderate activity. Admitted on account of acute pain in region of right costal border, of sudden onset in a movement of alarm; it was the first time that pain had been severe.

He was a stout heavy man with a pendulous abdomen. The origin of the pain, which was referred over the whole right side of the chest and forward into the right breast was an exquisitely tender nodule, which was palpable in the neighbourhood of the intersection of the costal margin and the sacrospinalis muscle. He seemed to be in great pain and could not lie down in bed. He sat in a chair for three nights, needing morphia on two occasions. On the third day an incision was made over the nodule which had been transfixed. Yellow subcutaneous fat was seen for a depth of about $\frac{1}{2}$ in., and imbedded in this was a white shiny balloon of oedematous fat. A fibrous band was found constricting it at its origin, which seemed to be the remains of the partition of a loculus through which the lobule had herniated and become strangulated. This was removed, and the patient had no further pain in this region, although 'fibrositic' pains were subsequently complained of elsewhere.

Case 3. Aged 40 years. (The lateral type of hernia.)

No previous rheumatic history. A four weeks history of severe pain in the left buttock radiating down the back of the thigh to the ankle. He had been in hospital under treatment for a month with no improvement. He attributed the onset to sleeping on a cold concrete floor.

Well developed man. No tenderness or wasting of thigh. Lasègue's sign positive. Reflexes present. A localized point of tenderness was found in left buttock two inches below the iliac crest and four inches from the midline. Pressure on this reproduced the sciatica. Other tender points were found, but did not produce such pain on pressure. An incision was made over this point, and on dividing the superficial fascia a large fat lobule which had evidently been under considerable pressure welled up into the wound. When this was pulled upon the sciatica was reproduced. Its origin was found to be in an adjoining compartment of fibrous tissue, from which it had herniated through the side wall. A cavity about the size of a cherry was left after it had been removed. Deep pressure in and around this cavity failed to provoke any further sciatic pain, and when he was seen a month later there had been no recurrence.

Case 4. Aged 27 years. (Multiple non-pedunculated herniae.)

No relevant history until two and a half years before, when he had suffered from severe backache of sudden onset. This was treated with heat and massage and recovered in a few days. Admitted to hospital with infective hepatitis and on the fourth day pain recurred severely in the same place, lasting for four days. It then disappeared for two days, but returned.

A very tender palpable nodule about the size of a small pea was found on the border of the right sacrospinalis muscle $1\frac{1}{4}$ in. above the iliac crest. An incision was made, the fat in the superficial fascia appeared to be under considerable pressure at all levels, and a series of small herniations were

observed of which the palpable nodule was only the culminating point. The fibrous walls of the fat lobules were unusually firm and where the herniating lobules passed between them, obvious constriction could be seen. Many of these were divided, a few fat lobules removed, and the area 'teased'. When the wound had been stitched there was seen to be a hollowing of the area around. This must have resulted from the release of local tension, as the amount of fat removed bore no relationship to the degree of sinking of the tissues in this spot. Two days later this was no longer obvious. The patient stated immediately after operation that the rheumatic pain had gone, although the wound was sore. He had no further trouble.

Pedunculated Type

Case 5. Aged 32 years. (Case of pedunculated hernia.)

He had suffered since 1928 with severe pain in the back, which had occurred first after a football accident. The pain had been much worse at times and he had seldom been entirely free. He had had much physical treatment, but this had always had to be stopped, as it made the pain worse. In 1933 it was diagnosed as a fibrositic nodule, and he was told that he would always have it. Weather appeared to affect it, and if he caught a cold it generally became almost unbearable for a few days. He had been in hospital twice with it, and sometimes it woke him up in the early mornings, but the pain then generally passed off if he got out of bed and took a few deep breaths. The present attack was started by a mild attack of jaundice.

An incision was made at the site of the palpable nodule, which lay just below the right iliac crest four inches from the midline. A congested looking fat lobule was found lying superficial to the fascia and a vascular pedicle which contained two small blood-vessels and showed some evidence of torsion, was found leading downwards through the fascia to another rather larger lobule, which was lying deeply amongst, but distinct from, the rest of the fat normally present in this area.

Compression of the superficial nodule before removal reproduced the pain complained of, but this never recurred subsequently (Fig. 5).

Case 6. Aged 32 years. (Case of pedunculated hernia.)

No previous rheumatic history. The first onset of severe pain in the back was in 1939, when he slept on the ground whilst suffering from an attack of influenza. The pain gradually got better, and at the end of six months it disappeared for a period of 18 months. It reappeared with a severe cold in 1942, and since then had been very painful. During the previous few months the pain from this spot had been radiating down the back of the leg into the outer aspect of the calf. He had been in hospital and had had physical treatment of various sorts without benefit. At times he found it difficult to walk, whilst at all times he did so with a limp.

A very tender palpable nodule was found on the left iliac crest three inches from the midline. On being pressed this reproduced the sciatica. Whilst this pain was present the tendon of the semimembranosus muscle was also generally found to be tender. 'Valleix's points' were all present and Lasègue's sign was positive and gave rise to great pain. The reflexes were elicited with difficulty and there were no sensory abormalities.

On incision of the skin and subcutaneous tissues, a tense fat lobule about the size of a small cherry was found lying superficial to the fascia. A short pedicle containing blood-vessels was seen connecting this with two other

lobules which lay beneath the fascia also under tension. These were teased out (causing considerable pain) and the superficial lobule was removed. No further pain occurred. One month later the patient was seen, and was entirely free from symptoms.

Case 7. Aged 28 years. (Case of bubble type of non-pedunculated hernia.)

No previous or family history of rheumatism. No serious illness. Was a gardener in civil life, and suffered with severe lumbago on one occasion three years before for 7 to 10 days.

Eighteen months before, this occurred again in the same place, lasting 10 to 12 days and clearing up with heat and massage. It also occurred in the shoulders on this occasion. Ten days prior to admission, further sudden onset of pain in lumbar region, all over the back at first, but later chiefly in one spot.

Very tender nodules found in the left gluteal region about one inch below the crest of the ilium, and at the outer border of right sacrospinalis muscle two inches above iliac crest. The temperature, white cell count, and blood sedimentation rate were normal.

The nodule having been transfixed with a needle, an incision was made at the outer border of the sacrospinalis muscle. The deep fascia was explored and several herniations were seen, looking like bubbles. These had tense fat in them, which was continuous with that in the angle of the fascia. There was also a tense-looking fat lobule lying just external to these, in the lumbar pad, and superficial to the deep fascia. This tracked downwards and outwards and, when it was pulled, seemed also to give rise to the pain complained of. This and a few neighbouring fat lobules were removed, the bubbles were opened, and the contained fat 'teased'. There was no further recurrence of any pain in the back and he was discharged well three weeks later.

Case 8. Aged 30 years. (A similar case.)

The only medical history was of occasional colds and influenza. In 1942 he had suffered with lumbago and was in bed 11 days. He was not much better when discharged from hospital in spite of treatment, but after three to four weeks on light duty he recovered. The present attack started suddenly 16 days previous to admission, but he thought in a different part of his back from the previous attack. His medical officer had found three trigger points which intensified the pain on pressure, and these were successfully injected. He then went back to driving a lorry which vibrated excessively. Two days later he slipped whilst starting the lorry and hit his back. This brought back the pain in the same place as before.

A very tender spot was found at the edge of right sacrospinalis muscle, 2½ in. above the iliac crest. No nodule was palpable. The marks of previous injections were seen ½ in. above this point.

An incision was made, and a finger inserted could feel nothing, although pressure reproduced the pain. The deep fascia was exposed, and a small bubble herniation which felt tense was seen. This was removed, together with the surrounding area of fascia. The underlying muscle was carefully inspected and palpated, with negative result. The incision was prolonged upwards, and similar herniations were found at the site of the previous injections which had given relief. These seemed to be less tense and were not removed. The patient was cured by this procedure.

Foraminal Type

Case 9. Aged 38 years. (Foraminal type of hernia.)

No previous rheumatic history. No serious illness. He had wrenched his back, was seized with a sudden very severe pain in the left lumbar region, and could not straighten his back. He was in hospital for three months and many types of treatment were tried, including procaine injections and physical medicine. Towards the end of this period he gradually got better. Since then pain had returned occasionally, but less severely. He was often conscious of it on waking if he had been sleeping on his right side. The pain gradually wore off with exercise.

A very tender spot was found at the outer border of the left sacrospinalis muscle, one inch above the crest of ilium. No nodule was felt, but the pain on pressure was severe and localized. The spot was transfixed at depth of one inch from the surface, and incision was made through the underlying fat to the edge of the muscle. Here a small, highly vascular tuft of fat was seen, presenting through the fascial foramen of the second lumbar nerve, together with the nerve and two small blood-vessels. When this was pulled upon, the pain was reproduced sharply. When the nerve itself was pulled upon, and finally cut, the pain was described as being of a pricking character, quite different from that complained of, and it was also referred round to the front of the body. After the removal of this fat and the enlargement of the foramen, the patient has been completely free from pain for the first time for three months. He was discharged well three weeks later (Plate 1, Fig. 6).

Case 10. Aged 42 years. (Foraminal type of hernia.)

No serious past illness. Fifteen years ago he had had an appendicectomy under a general anaesthetic, and since then had had almost continuous backache, becoming worse during severe exertion, or when he was very tired. If he caught influenza or a cold, it became very painful during the febrile period. He had had much massage and physical treatment.

A very tender spot was found at the border of the right sacrospinalis muscle, one inch above the iliac crest. This was transfixed at a depth of $1\frac{1}{4}$ in. An incision was made, the deep fascia was exposed, and a small lobule of reddish fat was found to be herniating through a patent nerve foramen at this point. This was removed, reproducing the pain during the process, and the foramen was enlarged. The lobule was found to be continuous with the deep basic fat, lying in the angle of the fascia, where it splits to enclose the muscle. The patient had no subsequent recurrence of pain in this region.

Histology. Microscopically the 'nodules' which were removed at the biopsies consisted principally of fatty tissue with young cellular fibrous tissue growing into it. The blood-vessels were congested, and their walls thickened, with perivascular proliferation. There were also in some nodules occasional patches of older fibrous tissue.

Discussion

It is probable that the anatomical conditions which we have described represent a comparatively advanced stage in the process and that, to explain the minor and less localized degrees of fibrositis almost universally

experienced at one time or another, we need not postulate actual herniation of the fat tissue.

It seems reasonable to suggest that the pain in fibrositis is due to a temporary or permanent increase in tension in fat which is confined within a non-distensible fibrous covering or sheath, a condition which obtains anatomically principally along the borders of the muscles which maintain the erect posture, that is, in the basic fat pattern. Cases have been seen in which the whole of this pattern was actually tender, and in one very thin patient (during the pyrexial period of infective hepatitis) it could actually be seen bulging beneath the skin. It is suggested that it is in the fat, rather than in the investing fibrous tissue, that the pain arises, because in the specimens examined the terminal arborizations of nerve fibrils were found more often in the fat lobules. Fat is structurally the most primitive of tissues and easily becomes oedematous if its blood-supply is defective. This excess of fluid is normally removed through the lymphatic system, and it thus seems that it is on the efficient working of this system that the natural resolution of fibrositis in its earlier stages may depend. If for any reason, such as prolonged rest in bed, the normal mechanism is rendered inefficient, the tension in the fat lobules may gradually increase, and a progressive tendency to herniation at the weakest points of the investing fascia will ultimately localize the painful process at these points, with the eventual formation of palpable nodules.

Treatment by 'teasing'. Our observations at biopsy led us to evolve a technique which we call 'teasing' the nodule. This consists in anaesthetizing a small area of skin over the site of the trigger point which has previously been ringed with a skin pencil. It is then transfixed with a stout rigid needle, and after injection of 10 to 20 c.c. of 1 per cent. procaine solution under the greatest pressure possible, the point of the needle is swept round deeply in such a way as to undercut the nodule, much as a tenotomy knife might be used, in an attempt to divide the pedicle of the herniated portion should there be one, and also to disrupt any neighbouring lobules which may be sharing in the congestion. By the use of this method, which must be tempered with a knowledge of the anatomical formation of the area being treated, we have achieved more lasting results than with the normal technique of injection.

Summary

(1) A study of 'fibrositis' of the back has been made. The pain has been studied clinically and the occurrence of trigger points confirmed. The exact situation in which these occurred in a large number of patients was charted, and a pain pattern of definite shape obtained.

(2) Our previous observation that these points may arise during any pyrexial illness or as the result of trauma was confirmed, also that the subjective pain disappears, but the point often remains and can be detected by tenderness on palpation. It can be reactivated subsequently, and may gradually become the seat of chronic pain.

(3) The back was carefully dissected in 14 bodies with particular reference to the chief sites of pain. It was found that a basic fat pattern was constantly present, even in the most cachectic subjects in whom all other fat was absent. This fat pattern was observed to correspond exactly in shape and situation with the pain pattern already charted.

(4) No lesions suggestive of inflammatory reaction were found in any deep fibrous tissue, but certain interesting abnormalities affecting the lobules of the fat pattern were found on several occasions. The abnormality which seemed most likely to have clinical significance was the herniation of certain fat lobules, through weaknesses or actual deficiencies in the walls of their investing fibrous tissue. It was considered eventually that these fat herniae should be regarded as pathological only in certain circumstances. They have been classified into three types.

(5) In the dorsal region it was noted that fibrositic pain which occurs a few inches either side of the spine differed in certain respects from that occurring elsewhere in the back. As a result of this a different origin was postulated, and this received confirmation from the dissections.

(6) A series of 10 biopsies on selected patients suffering from fibrositis were carried out, and these are reported in full.

(7) Although it is thought that the lesions described here (we believe for the first time) may be causative of the pain in the established cases of fibrositis and incidentally provide the explanation for its sudden onset in many cases, it is believed that its basic origin lies in an increase of tension in the fat lobules affected where they are invested by a non-distensible fibrous membrane. This circumstance occurs most importantly in the basic fat areas described. The anatomical lesions described in this paper are probably a late result of this condition where it persists.

Our thanks are due to Major W. H. Mylechreest for the provision of post-mortem facilities and for cutting sections of the biopsy material.

FIG. 4. Non-pedunculated type of fat hernia (Case 1)

FIG. 5. Pedunculated type of fat hernia (Case 5)

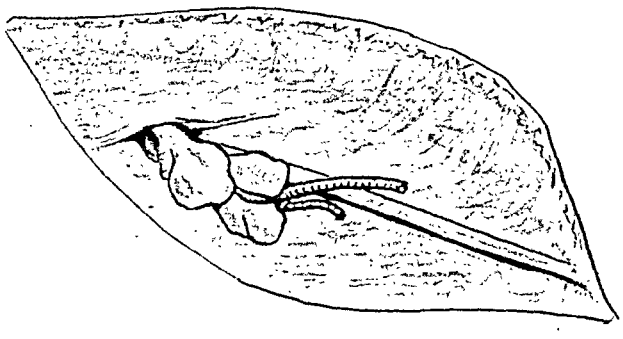

FIG. 6. Foraminal type of fat hernia (Case 9)
Note nerve and vessels

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PROTEOLYSED LIVER IN THE TREATMENT OF REFRACTORY ANAEMIAS[1]

By L. J. DAVIS and L. S. P. DAVIDSON

(From the Department of Medicine, University of Edinburgh)

Introduction

Proteolysed liver, a papain digest of whole liver suitable for oral administration, was described by Davis, Davidson, Riding, and Shaw (1943) and shown in a preliminary investigation to be effective in the treatment of cases of Addisonian pernicious anaemia. The present communication is concerned with its clinical trial in certain cases of severe anaemia refractory to treatment with potent liver extracts administered parenterally. Our observations during the past two years on a number of such cases of refractory anaemia have led us to the conclusion that proteolysed liver is an effective therapeutic agent in anaemias with cellular megaloblastic bone marrows, but that it is of no benefit in idiopathic aplastic anaemias with hypocellular normoblastic marrows, as revealed by sternal puncture.

The classification of refractory anaemias on the basis of sternal marrow morphology has recently been discussed by Davidson, Davis, and Innes (1943) and will not be considered in further detail here. Since the term 'megaloblast' is not free from ambiguity, it is perhaps desirable to state that in the present paper the description of a marrow smear as megaloblastic connotes an appearance identical with that seen in cases of Addisonian pernicious anaemia in relapse. In such smears, suitably stained, a high proportion of the erythroblasts are large cells with abundant dark-blue cytoplasm and large nuclei displaying a finely reticulated structure in which nucleolar remnants may or may not be seen. Many of the more mature red-cell precursors which show varying degrees of haemoglobination are distinguished from normoblasts by their relatively greater size and particularly by the loosely woven character of the nuclear chromatin (illustrations are given in the paper by Davidson, Davis, and Innes, 1943).

Of a series of refractory anaemias with megaloblastic sternal marrows successfully treated with proteolysed liver, five representative examples are presented in the present paper. The patients concerned were an elderly woman, a child, a middle-aged man, a young man, and a young woman in the puerperium. We have also studied three cases of severe refractory macrocytic anaemia of obscure origin in which proteolysed liver therapy

[1] Received July 15, 1944.

resulted in partial blood regeneration and clinical improvement. In these cases the sternal marrow films showed a 'dimorphic' picture in that the majority of the red-cell specimens were typical normoblasts with dense nuclear chromatin, but primitive basophilic erythroblasts were unusually numerous, and a small proportion of the maturing cells showing partial haemoglobination had the open-work nuclear structure of late megaloblasts. The term 'dimorphic anaemia' was introduced by Trowell (1942) to embrace anaemias encountered in the tropics due to the dual deficiency of liver principle and iron, resulting in a peripheral blood picture displaying both macrocytosis and hypochromia. In our cases the peripheral blood picture afforded no evidence of an iron deficiency, but we consider the term 'dimorphic' to be a convenient provisional designation for sternal marrow films showing erythropoiesis which is predominantly normoblastic but partially megaloblastic. Finally we have observed five cases of idiopathic refractory anaemia with hypocellular normoblastic bone marrows (aplastic anaemia) all of which failed to show any evidence of a haematopoietic response to prolonged treatment with proteolysed liver or any other form of haematinic therapy.

It should be noted that the test parenteral liver extract referred to in the present paper was in each case 'Anahaemin' from batches the potency of which had been confirmed by us and shown, in a single dose of 2 c.c., to produce a satisfactory reticulocyte response and rise in the red-cell count in cases of Addisonian pernicious anaemia.

Case Reports

Refractory macrocytic anaemias with megaloblastic erythropoiesis.

Case 1. A married woman aged 56 years. The patient, who had been suffering from fatigue and breathlessness during the past two years, was admitted to hospital on 1.2.1944. Apart from the usual manifestations of severe anaemia, no abnormalities were detected on physical examination, but the patient was underweight. There was no diarrhoea.

Laboratory findings. Haemoglobin 22 per cent., red cells 840,000 per c.mm., colour index 1·30, and white cells 4,800 per c.mm. Blood films showed marked anisocytosis, poikilocytosis, and numerous macrocytes. Reticulocytes were less than one per cent. Gastric analysis revealed a histamine-fast achlorhydria. Radiological examination of the thorax and alimentary tract was negative. The fat content of the stools was within normal limits, and there was no evidence of occult blood. Examination of the urine revealed no significant abnormalities. The Wassermann reaction was negative.

Progress. The patient was given a transfusion of 1 pint of whole blood, treated with iron and ascorbic acid by mouth, and given injections of 'Anahaemin' twice weekly, receiving a total 28 c.c. during the ensuing five weeks. This treatment resulted in no significant improvement in her haematological condition and when seen by us on 13.3.1944 her haemoglobin was 30 per cent., with 1,160,000 red cells and 3,000 white cells per c.mm. The mean cell volume was 108 c.μ and the blood picture macrocytic. A sternal puncture performed at this time showed a typical megaloblastic marrow. Parenteral liver therapy was stopped and proteolysed liver given

by mouth. Reference to Fig. 1 will show that this treatment was followed by a reticulocyte response of 18·6 per cent. on the ninth day, and by a rise in the blood count, which was accompanied by a striking improvement in the patient's clinical condition. It should be noted that there was a rise in red cells of 1,440,000 per c.mm. during the first 14 days of treatment.

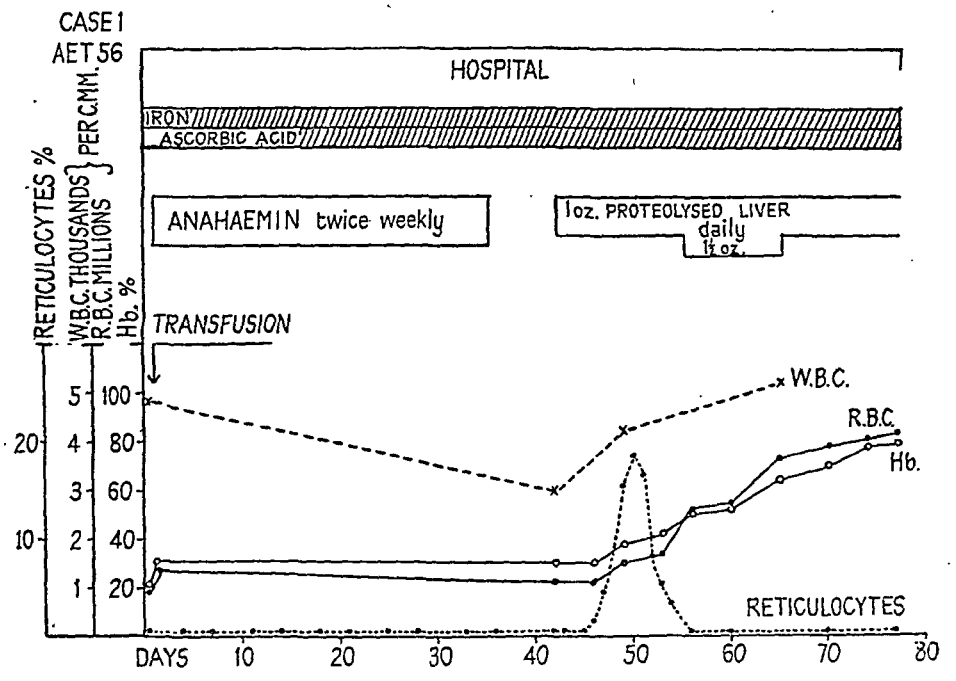

FIG. 1. Case 1, megaloblastic anaemia in an elderly woman

The patient was discharged from hospital five weeks after commencing the proteolysed liver therapy with 78 per cent. haemoglobin and 4,180,000 red cells per c.mm. It was arranged that she should continue to take proteolysed liver at home. When last seen, a fortnight after leaving hospital, her red-cell count had risen to 4,400,000 per c.mm.

Comment. The evidence in this case, that proteolysed liver succeeded where parenteral liver extracts failed is, we submit, clear-cut and conclusive. From the available data it appears that this case presents no features incompatible with a diagnosis of classical Addisonian pernicious anaemia, apart from the failure to respond to liver extract. Accordingly the term refractory pernicious anaemia seems an appropriate designation. It remains to be seen whether maintenance treatment with proteolysed liver will need to be continued permanently.

Case 2. This patient, aged 12 years, was a healthy, well-nourished, energetic girl until two months preceding admission to hospital when a progressive loss of weight and energy and increasing pallor were noted. During the previous fortnight the patient became confined to bed and developed a cough and headaches. There was no history of diarrhoea or coeliac disease. On admission to hospital on 12.8.1943, the patient who weighed 5 st. was found

to be pale and listless. The liver was firm but not tender, and its lower edge extended one inch below the costal margin. Enlargement of the spleen and lymph glands was not detected. The tongue was clean, moist, and not smooth. The gums were soft, spongy, and bled easily. No evidence of purpura or jaundice was noted. No diarrhoea was present and the stools had

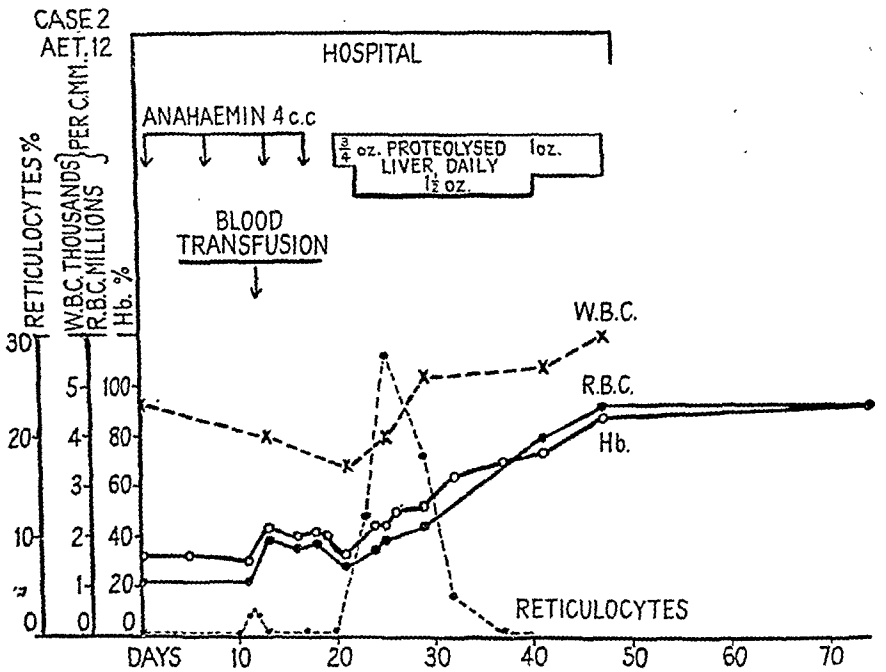

FIG. 2. Case 2, megaloblastic anaemia in a 12 year old girl

a normal appearance. Radiological examination of the chest was negative, but confirmed the enlargement of the liver.

Laboratory findings. Examination of the blood revealed a macrocytic anaemia with pronounced anisocytosis and poikilocytosis with numerous large macrocytes. The red-cell count was 1,130,000 per c.mm., haemoglobin 32 per cent., colour index 1·42, reticulocytes less than 1 per cent., and white cells, 4,600 per c.mm. Sternal puncture showed a typical megaloblastic marrow picture. The Wassermann reaction was negative. The gastric juice contained free hydrochloric acid. The icteric index was 13; no excess of urobilinogen was present in the urine. The stools were repeatedly examined for occult blood with negative results, and a fat analysis showed 13·5 per cent. total fats of which 71·4 per cent. was split.

Progress. An injection of 'Anahaemin' 4 c.c. was given and repeated after six days with no evidence of any haematopoietic response. Five days after the second injection the haemoglobin fell to 30 per cent. and the patient developed a retinal haemorrhage. A blood-transfusion of one pint was given which raised the haemoglobin to 44 per cent., and was followed by two more injections of 'Anahaemin' 4 c.c., without response, the haemoglobin falling to 32 per cent. four days after the last injection. The patient was then given proteolysed liver by mouth working up to 1½ oz. daily. This was followed by a reticulocyte count of 28 per cent. on the fifth day after commencement of this form of therapy, and a progressive clinical and haematological improvement (see Fig. 2). Twenty-seven days after commencing the proteolysed

liver treatment, the red-cell count was 4,500,000 per c.mm., haemoglobin 85 per cent., colour index 0·94, and the white-cell count 6,000 per c.mm. The patient's general condition was considerably improved and she had gained 10 lb. in weight since admission to hospital. She was accordingly discharged home and did not receive any further liver or any other haematinic treatment. When seen four weeks later she was feeling very well and her blood picture was normal, the red-cell count being 4,500,000 per c.mm., with haemoglobin 90 per cent. The lower edge of the liver was just palpable and was neither firm nor tender. Two months later her haemoglobin was 100 per cent., with 4,900,000 red cells per c.mm. and her general health was excellent, and has remained so during recent months.

Comment. This case is difficult to classify on an aetiological basis. There was no evidence of nutritional deficiency or of alimentary disorder, while the age of the patient, the presence of free hydrochloric acid in the gastric juice, and the lack of response to liver extract serve to distinguish it from Addisonian pernicious anaemia. It may be noted that two other cases of megaloblastic anaemia in children have recently been studied by us. One of these was also refractory to parenteral liver extracts, but responded to proteolysed liver. Details will be published elsewhere (Davis, 1944). We consider that this case provides an unequivocal example of the success of proteolysed liver therapy after the failure of injections of liver extract during the preceding period of 20 days.

Case 3. A man aged 47 years. This patient, by occupation a colliery fireman, gave a history of severe dysentery incurred during military service in 1918 which eventually responded to treatment with no subsequent relapses. During the past few years he had suffered from chronic nasal catarrh and from indigestion for the relief of which he had been in the habit of taking alkaline powders. He had been able to do his work until June, 1942, when he began to suffer from fatigue, breathlessness, and a sore tongue. At this time he also had several attacks of diarrhoea which ceased after a few weeks and did not recur. During the ensuing nine months the fatigue became worse, swelling of the ankles developed, and the patient lost one stone in weight. He was first admitted to hospital in March, 1943, with the symptoms and signs of a severe anaemia. Apart from a red smooth tongue and a mild degree of icterus, no other significant abnormalities were noted.

Laboratory findings. Haemoglobin 36 per cent., red-cell count 1,240,000 per c.mm., mean cell volume 133 c.μ, colour index 1·45, reticulocytes less than 1 per cent., and white-cell count 2,600 per c.mm. Inspection of blood films showed the classical picture of pernicious anaemia with numerous oval macrocytes. Sternal puncture revealed a typical megaloblastic marrow picture. The icteric index was 13. A test meal showed free hydrochloric acid to be present in the gastric juice. Radiological examination provided no evidence of any organic lesion of the alimentary tract.

Progress. The patient was given weekly injections of 'Anahaemin' 2 c.c. which resulted in a reticulocyte response of 18 per cent. on the tenth day after commencement of treatment, and a moderate rise in the red- and white-cell counts. A month after admission to hospital, however, the red-cell count was only 2,400,000 per c.mm. with 57 per cent. haemoglobin. After his discharge from hospital, the patient continued to receive weekly injections of 'Anahaemin' together with iron by mouth, but the red-cell

count remained stationary and some months later began to deteriorate in spite of the continuance of the injections of liver extract.

The patient was readmitted to hospital in February, 1944, when his red-cell count was found to be 960,000 per c.mm., with 26 per cent. haemoglobin. The blood picture was macrocytic with a mean cell volume of 115 c.μ, the

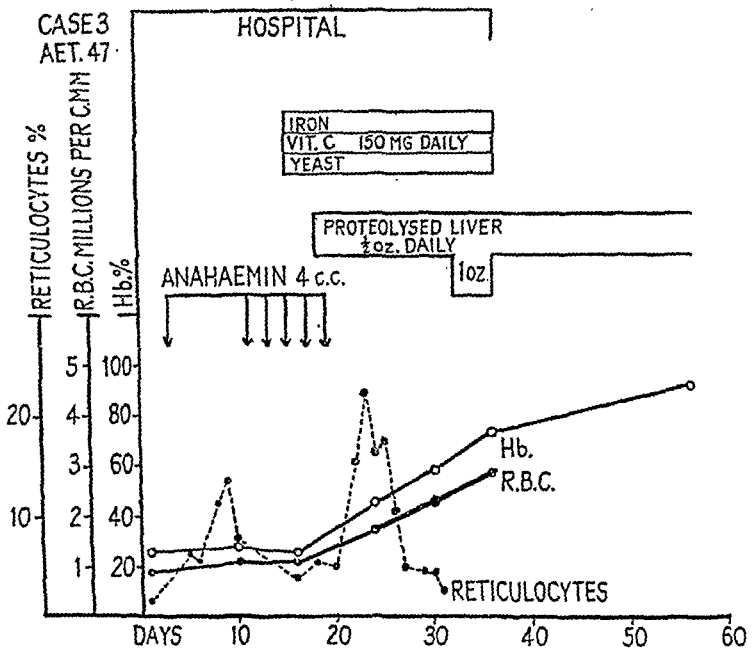

FIG. 3. Case 3, megaloblastic anaemia in a middle-aged man, second admission to hospital, February 1944

sternal marrow was still megaloblastic, and free hydrochloric acid was present in the gastric juice. The progress of the patient during this second stay in hospital is shown in Fig. 3. It will be seen that although the first injection of 4 c.c. of 'Anahaemin' was followed by a reticulocyte response of 13·5 per cent., neither this nor subsequent injections of 'Anahaemin' resulted in a significant rise in the red-cell count. The administration of proteolysed liver, however, was followed by a second reticulocyte response of 22 per cent. and rapid regeneration of red cells. The patient left hospital 18 days after commencing to take proteolysed liver, with a red-cell count of 2,850,000 per c.mm. and 74 per cent. haemoglobin. He continued to take proteolysed liver daily at home and reported back three weeks later with 90 per cent. haemoglobin. After a further five weeks his blood count was normal.

Comment. It is unfortunate that in this case, through circumstances beyond our control, the therapeutic experiment was marred by the failure to interpolate a control period between the cessation of the parenteral treatment and the commencement of proteolysed liver, and by the administration of iron, ascorbic acid, and yeast tablets ('D.C.L.') at about the same time that proteolysed liver was given.

In view of the unsatisfactory haematopoietic response to 'Anahaemin' given weekly prior to readmission to hospital and to the first four injections

during the first 15 days after readmission, it is reasonable to assume that the subsequent response cannot be attributed to these injections.

We feel more dubious concerning the possible significance of the ascorbic acid, since it has been claimed by Dyke, Della Vida, and Delikat (1942) that the administration of this vitamin may, in certain circumstances, be necessary for the effective action of liver extracts. It should be noted that Minot and Castle (1943) do not agree that the evidence presented by the former authors warrants the conclusions drawn by them. We may add in parenthesis that we have never encountered a case of Addisonian pernicious anaemia, either before or during the present war, in which dietary deficiency of vitamin C could be held responsible for an inadequate response to a potent liver extract. Furthermore it should be noted that we have never observed any significant haematopoietic response in cases of refractory anaemia, other than in those due to scurvy, which could be attributed to ample supplements of ascorbic acid.

The significance of the iron can safely be discounted since it is manifest from our own experience and from that of others that the administration of this element is ineffectual in the initial treatment of megaloblastic anaemias, refractory or otherwise.

It is highly probable that the administration of yeast can also safely be discounted since, in the dosage employed of six 'D.C.L.' tablets daily, it was equivalent only to aneurin 2 mg., riboflavin 0·1 mg., and nicotinic acid 0·6 mg. Neither in our previous studies on refractory anaemias (Davidson, Davis, and Innes, 1943) nor in observations on cases of pernicious anaemia have we observed any response to the administration of yeast, even in large doses, comparable with that observed in the present case.

Case 4. A man, aged 21 years, was admitted to hospital on 10.5.1944 with symptoms of severe anaemia. At the age of 17 years his cervical lymph glands had become enlarged. The swellings subsequently subsided, but reappeared the following year. No diagnosis was definitely established, but X-ray treatment was given and resulted in the regression of the lymphadenopathy. At the age of 19 years he developed a severe anaemia. Details are not available, but we are informed by his doctor that a diagnosis of aleukaemic leukaemia was suggested. However, treatment with injections of liver extract and iron by mouth resulted in clinical and haematological improvement, so that when seen by one of us three months later his blood count was as follows—haemoglobin 60 per cent., red cells 3,520,000 per c.mm., and white cells 3,800 per c.mm. A sternal puncture was done, but revealed no abnormal features. The patient's condition continued to improve and he remained well until early in 1944 when his condition deteriorated so that he had to give up his work, which was clerical, and the anaemia progressed in spite of numerous injections of 'Anahaemin', with iron and vitamin concentrates by mouth. There was no history of vomiting, steatorrhoea, or other manifestations of alimentary disorder. His father had died of pernicious anaemia. On examination, he was a pale, poorly developed lad. There was no evidence of enlargement of the liver, spleen, or lymph glands. No signs of jaundice or petechial haemorrhages were seen. The tongue was clean and moist. No other abnormalities were detected clinically.

Laboratory findings. Examination of blood-films revealed a macrocytic picture with ovalocytosis and a few normoblasts. No abnormal white cells were seen. The haemoglobin was 50 per cent., red cells 2,280,000 per c.mm., colour index 1·1, mean cell volume 105 c.μ, mean cell diameter (by halometer) 8·4 μ, reticulocytes 4·8 per cent., and white cells 7,400 per c.mm.

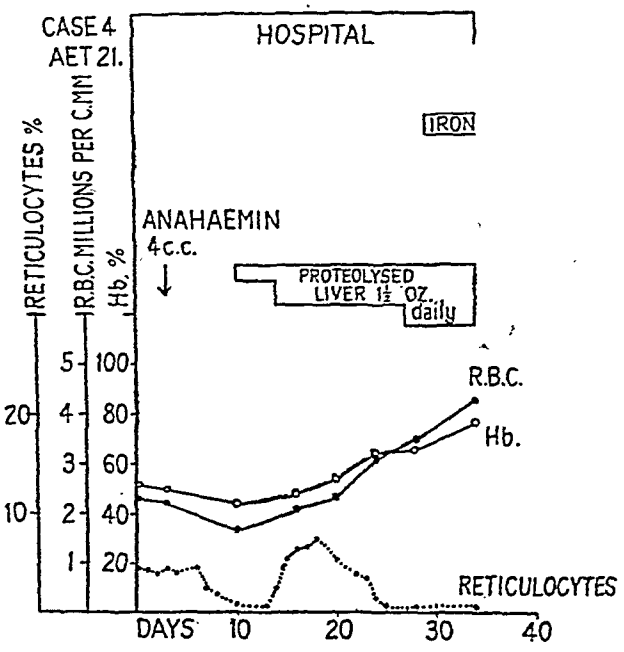

FIG. 4. Case 4, megaloblastic anaemia in a young man

Red-cell fragility, normal. Bleeding time, 5 min. Coagulation time (Lee and White), 8 min. Sternal puncture revealed a cellular megaloblastic marrow. The nuclear structure of some of the erythroblasts was slightly denser than that seen in Addisonian pernicious anaemia in the stage of severe relapse, but in others the open character of the nuclear chromatin left no room for doubt that erythropoiesis was predominantly megaloblastic. Gastric analysis showed free hydrochloric acid in the gastric juice. The icteric index was 7. The Wassermann reaction was negative. Urine—urobilinogen present, but no other abnormal constituents noted.

Progress. Although the patient had received numerous injections of liver extract immediately prior to his admission to hospital, he was given a test dose of 'Anahaemin' 4 c.c., but no erythropoietic response resulted. The reticulocyte count persisted at about four per cent. for a few days, but within a week it fell to less than one per cent., by which time the red-cell count had fallen to 1,770,000 per c.mm. Proteolysed liver therapy was then commenced, starting with 3 drachms daily, and working up to 1½ ounces. A rapid improvement in the patient's clinical and haematological condition was soon noticed, the red-cell counts rising to 2,100,000 per c.mm. on the sixth day and 3,200,000 on the fourteenth day after commencement of treatment (see Fig. 4). No abrupt reticulocyte response was noted, the maximum count of 7·2 per cent. occurring on the eighth day. The patient was discharged from hospital on 12.6.1944 after 24 days of proteolysed liver therapy, with a red-cell count of 4,280,000 per c.mm. and 78 per cent. haemoglobin, having gained 9 lb. in weight, and feeling very well.

Comment. The pathogenesis of this case is obscure. When first seen the persistently elevated reticulocyte count of about four per cent. and the urobilinuria were thought to be suggestive of a haemolytic disorder, but the absence of hyperbilirubinaemia and any history of jaundice and the normal red-cell fragility rendered such a condition unlikely. It may be noted in this connexion that in our experience a persistent low-grade reticulocytosis of this order may occasionally be encountered in severe dyshaematopoietic anaemias.

The earlier history of lymphadenopathy which responded to X-ray treatment is suggestive of a reticulosis or leukaemia, but no biopsy was done and when the patient was seen by us there was no evidence of these disorders. In view of the presence of free hydrochloric acid in the gastric juice it is unlikely that this was a case of Addisonian pernicious anaemia. The record of this patient leaves no reason to doubt the refractory nature of the case in view of the failure to respond to numerous injections of 'Anahaemin' supplemented by iron and vitamins. The subsequent immediate and vigorous response to proteolysed liver accordingly provides conclusive evidence of its therapeutic efficacy. It remains to be seen whether liver therapy will be required to be maintained permanently in this case.

Case 5. A married woman, aged 29 years, was admitted to a medical ward with symptoms of severe anaemia which had become manifest only since childbirth a month earlier. The confinement had been uncomplicated and there was no history of any abnormal or excessive haemorrhage. Three years previously she had also suffered from severe anaemia after a miscarriage and had been treated by transfusion, iron, and injections of liver extract, which however had not subsequently been continued. The patient was pale but not jaundiced. Her tongue was unduly red and smooth. A slight degree of cheilosis was present. No enlargement of liver, spleen, or lymph glands was evident. Menstruation had not recommenced since parturition and no source of blood loss was discovered.

Laboratory findings. Examination of the blood revealed a macrocytic anaemia, the haemoglobin being 33 per cent., red-cell count 1,190,000 per c.mm., colour index 1·34, reticulocytes less than 1 per cent., and white cells 3,200 per c.mm. A sternal puncture showed a typical megaloblastic marrow. Free hydrochloric acid was present in the gastric juice. The Wassermann reaction was negative.

Progress. Treatment with iron and ascorbic acid by mouth and two injections of 'Anahaemin' totalling 8 c.c. within two days resulted in no reticulocyte response, and a week later the haemoglobin had fallen to 18 per cent. Treatment with proteolysed liver, one ounce daily by mouth, was then commenced, and because of the patient's grave condition a transfusion of two pints of blood was given. Six days later a reticulocyte count of 7 per cent. was noted. Unfortunately subsequent reticulocyte counts were not made, but reference to Fig. 5 will show that a progressive rise in the haemoglobin and red-cell count ensued, the patient being discharged from hospital 17 days after the institution of proteolysed liver therapy, with a haemoglobin level of 70 per cent. After leaving hospital she continued on proteolysed liver at home for a month, by which time her blood condition had attained a normal level which has been maintained during the past eight months without further treatment.

Comment. This case is regarded as an example of refractory megaloblastic anaemia of pregnancy and the puerperium. Similar cases have previously been found by us (Davidson, Davis, and Innes 1942*a*) to respond eventually to intensive and prolonged treatment with parenteral liver extracts while life was sustained by blood transfusions. In the present case, however, the response to proteolysed liver was more prompt and rapid than we ever observed in our earlier series after intensive and prolonged liver extract therapy.

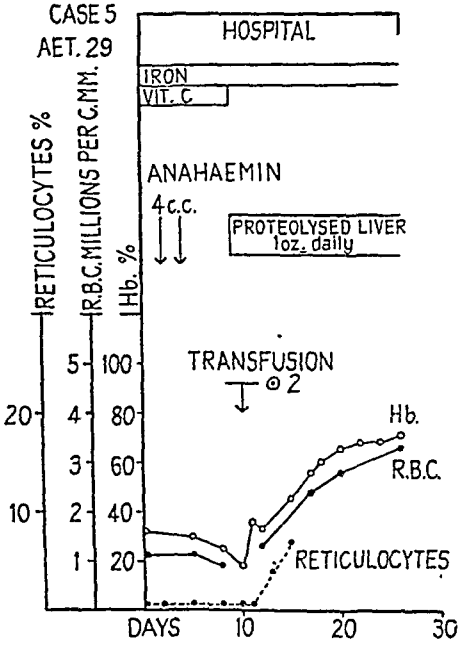

FIG. 5. Case 5, megaloblastic anaemia in the puerperium

It is regrettable that the immediate effect of the proteolysed liver was obscured by the blood-transfusion, but in the light of our previous experience with refractory megaloblastic anaemias (Davidson, Davis, and Innes, 1942*a*; 1943), we do not consider that the rapid haematopoietic response in this case can be attributed to transfusion.

Refractory macrocytic anaemias with 'dimorphic' erythropoiesis.

Case 6. A married woman, aged 76 years, was admitted to hospital on 17.3.1944, with symptoms of severe anaemia which had been progressively developing during the previous year. She had also lost weight during this period. Her previous personal and family medical history were not significant. Examination revealed no findings other than those attributable to anaemia. There was no jaundice, enlargement of liver, spleen, or lymph glands, or evidence of haemorrhage. Thorough investigations for malignant disease were negative.

Laboratory findings. Haemoglobin 22 per cent., red cells 970,000 per c.mm., colour index 1·13, reticulocytes less than 1 per cent., mean cell volume 105 c.μ, and white cells 2,000 per c.mm. Examination of blood films showed a macrocytic picture with marked anisocytosis and poikilocytosis. A granulopenia was evident, but no abnormal white cells were seen. Gastric analysis revealed a histamine-fast achlorhydria. Examination of the urine showed an increase of urobilinogen, and a trace of albumen. The Wassermann reaction was negative.

Progress. During the first 15 days in hospital the patient received three injections of 'Anahaemin' totalling 12 c.c. with no evidence of any response. Because of her severely anaemic state it was necessary to give her two blood-transfusions of two pints each, which raised her red-cell count to 2,100,000 per c.mm. A sternal puncture performed on 2.4.1944, after the last injection of 'Anahaemin', showed a cellular 'dimorphic' marrow picture. Most of the red-cell precursors were obvious normoblasts, but an undue proportion of primitive basophilic erythroblasts was seen and a few of the more mature cells displayed the open-work nuclear structure characteristic of megaloblasts. It was also noted that myelocytes were very numerous. On

the twentieth day of her stay in hospital the patient was put on proteolysed liver, 1 oz. daily. No significant reticulocyte response resulted, but there was a slow rise in the red-cell count and a definite improvement in the patient's clinical condition. After discharge from hospital the patient continued to take proteolysed liver and reported back 40 days after commencing this treatment feeling very well, with a blood count of—haemoglobin 74 per cent., red cells 3,780,000 per c.mm., and white cells, 7,200 per c.mm.

Comment. The peripheral blood picture and the achylia might warrant this case being diagnosed as Addisonian pernicious anaemia of a refractory type similar to Case 1. Such a view would entail the explanation that the 'dimorphic' appearance of the sternal marrow films resulted from the effect of the previous injections of liver extract. The objections to this explanation are dealt with later.

Case 7. A married woman, aged 65 years, was first seen by one of us on 28.11.1942. Manifestations of anaemia of increasing severity had been developing during the previous year. She had been treated for several months with iron by mouth and regular bi-weekly injections of liver extract ('Anahaemin') for two months, but her condition had continued to deteriorate. Examination revealed a well-covered woman with no obvious evidence of recent loss of weight, but displaying considerable pallor and a moderate degree of jaundice. The tongue was pale and smooth. The spleen was enlarged, extending 2 in. below the costal margin, and the liver was also moderately enlarged, the lower edge, which was smooth and firm, being palpable 3 in. below the costal margin. No other significant abnormalities were noted, apart from those to be expected in a state of severe anaemia.

Laboratory findings. There was a severe macrocytic anaemia, the count being as follows—haemoglobin 26 per cent., red cells 980,000 per c.mm., colour index 1·33, mean corpuscular volume 158 c.μ, reticulocytes less than 1 per cent., and white cells 2,000 per c.mm.; the differential count showing a granulopenia, but no abnormal or primitive cells. There was no thrombocytopenia. The red cells displayed marked auto-agglutination in the cold which rendered it necessary to keep the blood at body heat while the counts were being performed. In stained films the red cells displayed marked anisocytosis, macrocytosis, and poikilocytosis with ovalness of outline. Sternal puncture yielded only scanty flecks of marrow. The resulting smears were only moderately cellular and were mainly normoblastic, most of the red-cell precursors showing dense nuclear chromatin, but a few megaloblasts with open-work nuclei were seen.

Progress. The patient was given injections of 'Anahaemin' 4 c.c. on alternate days, with iron, ascorbic acid, and yeast by mouth. No reticulocyte response occurred, and by the tenth day her haemoglobin had fallen to 17 per cent. During the next week she was transfused with five pints of whole blood which raised the haemoglobin to 42 per cent. Haematinic therapy was continued, but when the patient was seen six weeks later the haemoglobin had fallen to 20 per cent. and auto-agglutination in the cold was still marked. She was again transfused, receiving the cells from six pints of blood during the ensuing week. The haemoglobin was thereby raised to 55 per cent., but by 6.2.1943 it had fallen again to 40 per cent. The patient was then sent home and received 'Anahaemin', 2 c.c. weekly, together with proteolysed liver $\frac{3}{4}$ oz. daily by mouth.

When next seen 10 weeks later on 22.4.1943, the patient showed a remarkable clinical improvement. The spleen was still palpable, but the liver could only just be felt on deep respiration. The haemoglobin was 60 per cent., red cells 2,210,000 per c.mm., colour index 1·3, and white cells 4,800 per c.mm. The red cells still showed macrocytosis, the mean cell diameter (by halometer) being 8·5 μ. Cold agglutination was no longer evident.

Six weeks later the patient was still feeling very well and the blood count was much the same. A sternal puncture performed at this time yielded abundant marrow flecks, and the smears were more cellular, being definitely 'dimorphic' in character. Large primitive basophilic erythroblasts were relatively numerous, and late megaloblasts with open-work nuclei were also seen. All therapy other than proteolysed liver was then stopped.

Some five weeks later the haemoglobin had risen to 70 per cent., with 3,000,000 red cells per c.mm. Proteolysed liver was then stopped. After two months without treatment the patient was still feeling and looking well, but the haemoglobin had fallen to 62 per cent., with 2,580,000 red cells and 2,200 white cells per c.mm., and the liver was again found to be enlarged. Proteolysed liver therapy was renewed for six weeks at the end of which time the haemoglobin had again risen to 70 per cent. with 2,910,000 red cells per c.mm.

Since it was thought desirable to determine, beyond doubt, the therapeutic significance of proteolysed liver, this medicament was again stopped, and replaced by a high protein diet supplemented by casein in the form of skimmed milk, with the object of ensuring an ample methionine content. After three months of this régime, however, the patient's condition had deteriorated; on 18.1.1944, the haemoglobin was 48 per cent., with 1,960,000 red cells and 2,200 white cells per c.mm. Auto-agglutination in the cold had reappeared. A third sternal puncture on this date revealed no change in the marrow picture from that seen on the last occasion.

The administration of proteolysed liver in doses as big as could conveniently be taken, 1 to 1½ oz. daily, was then resumed. Unfortunately a short time later the patient suffered from an influenzal attack with acute bronchitis and gastro-enteritis and when next seen, a month after the resumption of proteolysed liver therapy, her blood condition showed no improvement. She was given a blood-transfusion which raised her haemoglobin to 55 per cent., and proteolysed liver was continued. The further course of this patient is being observed.

Comment. The significant haematological findings in this case were the severe macrocytic anaemia in association with 'dimorphic' erythropoiesis. It will be noted that on the first occasion that sternal puncture was performed the resulting films were somewhat hypocellular. Whether this finding was fortuitous, in that a relatively hypoplastic patch of sternal marrow was sampled, it is impossible to say. However, the two subsequent sternal punctures, after the commencement of proteolysed liver therapy, both yielded cellular films in which the proportion of the erythroblasts of the primitive type was definitely higher than that found in a typical normoblastic marrow.

The pathogenesis of this case is quite obscure. The persistent enlargement of the liver and spleen constitutes a puzzling feature and is suggestive of some primary morbid condition of the former organ. It is possible that the

anaemic state resulted directly from hepatic dysfunction with consequent defective erythropoiesis. The suggestion that the anaemia was haemolytic in origin is not supported by the evidence. No persistent hyperbilirubinaemia or elevated reticulocyte count was noted.

Concerning the therapeutic aspects, there seems little reason to doubt that the administration of proteolysed liver resulted in the partial restoration of erythropoiesis. Although unfortunately this effect has latterly not been maintained, we consider that the prolongation of the patient's life for nearly two years, during most of which she has enjoyed relatively good health and been enabled to lead a happy and useful existence, is directly attributable to the administration of the proteolysed liver.

Case 8. A man, aged 58 years, was admitted to hospital on 14.2.1944, with the symptoms of severe anaemia. A year previously he had developed a severe anaemia for which he had been treated with injections of 'Anahaemin', together with iron and vitamin preparations by mouth. No satisfactory therapeutic response was obtained, but the patient survived, although shortly before his admission to hospital his condition deteriorated. On admission to hospital the patient, who was a thin, darkly pigmented man, was found to be desperately ill and suffering from persistent vomiting, dehydration, and extreme exhaustion. There was no enlargement of the liver, spleen, or lymph glands. Addison's disease was suspected, but appropriate laboratory and therapeutic tests did not support this diagnosis. Radiological and other investigations for malignant or other disease of the alimentary tract were negative. The benzidine test for occult blood in the faeces was repeatedly negative.

Laboratory findings. There was severe macrocytic anaemia, the data being as follows—haemoglobin 38 per cent., red cells 1,650,000 per c.mm., colour index 1·16, mean cell volume 115·2 c.μ, reticulocytes 1·4 per cent., and white cells 4,800 per c.mm.; no abnormal cells were seen. Sternal puncture revealed a cellular 'dimorphic' picture similar to that previously described. Gastric analysis showed free hydrochloric acid in the gastric juice.

Progress. Although the patient had received numerous injections of liver extract and iron by mouth preceding his admission to hospital, he was given a further test injection of 'Anahaemin' 4 c.c. with no response, the red-cell count falling to 1,370,000 per c.mm. three weeks later. During this time his condition underwent further deterioration. The dehydration was treated by saline infusions. Blood transfusions and vitamin supplements were also given, but he eventually sank to such a state of exhaustion that his life was despaired of.

The administration of proteolysed liver was then commenced in small doses. At first, the patient experienced difficulty in retaining it, but after a few days he succeeded in taking $\frac{3}{4}$ oz. daily. Vomiting then ceased and appetite was regained. Thereafter his clinical condition showed steady improvement and his red-cell count gradually rose to 1,930,000 c.mm., with 44 per cent. haemoglobin on 18.4.1944, some six weeks after the commencement of this treatment, but no reticulocyte response was noted. The patient was discharged from hospital and continued to take proteolysed liver. When seen two months later as an out-patient his clinical condition had greatly improved and he was feeling relatively well. His blood count was haemoglobin 48 per cent., red cells 1,970,000 per c.mm., and white cells 5,800 per c.mm.

Comment. The diagnosis of this case remains quite obscure. No adequate explanation was found for the severe exhaustion and vomiting or for the production of the anaemia. Although the haematological response to the proteolysed liver was poor, the physicians in charge of the patient were unanimous in their testimony that the improvement in the patient's clinical condition, and indeed his recovery from what was regarded as a moribund state, began only after the commencement of proteolysed liver therapy.

Refractory anaemias with hypocellular normoblastic marrows.

We have observed the effect of proteolysed liver therapy on five cases of anaemia of this type. In each case sternal puncture revealed a hypocellular marrow with normoblastic erythropoiesis, and the peripheral blood picture was normocytic with a granulopenia and thrombocytopenia. The cases accordingly merit the designation of aplastic anaemia. In respect of aetiology, one case was secondary to gold therapy in the course of rheumatoid arthritis, the remaining four were idiopathic, two occurring in middle-aged women, one in an elderly man, and one in a young man. Only the last will be described in detail.

In all cases treatment consisted of administration of the usual haematinic remedies including iron, vitamin preparations, and injections of liver extracts, while life was sustained by blood-transfusions. All the patients also received liberal doses of proteolysed liver over periods of weeks or months, but in no case was there evidence of blood regeneration. Four of the cases have terminated fatally, while one has so far survived in a state of severe anaemia. One example of this group will now be described.

Case 9. A man aged 27 years. The patient was an Army motor transport driver whose previous health had been satisfactory and who gave no history of exposure to toxic substances or of having received haemotoxic drugs. His illness had manifested itself by lassitude, pallor, headaches, impaired vision, and a tendency to bruising, all of which had developed during a period of five months preceding his admission to a military hospital.

His subsequent course will not be described in detail, but is depicted graphically in Fig. 6. It will be seen that during his stay in a military hospital he received frequent injections of liver extract and numerous blood transfusions. After two months in a military hospital the patient was transferred to a civil hospital under our care. The only abnormalities noted on physical examination were extreme pallor, numerous petechial haemorrhages, a retinal haemorrhage, and a slight degree of atrophy of the lingual papillae.

Laboratory findings. Haemoglobin 24 per cent., red cells 1,550,000 per c.mm., mean cell volume 93 c.μ, colour index 0·8, reticulocytes less than 1 per cent., and white cells 2,800 per c.mm., of which 30 per cent. were neutrophils, 65 per cent. lymphocytes, and 5 per cent. monocytes. Platelets were 40,000 per c.mm. The red-cell fragility was within normal limits, the bleeding time 12 min., and the coagulation time 6 min. Sternal marrow films showed only scanty cells with numerous fat spaces, but erythropoiesis could be recognized as being definitely normoblastic. The icteric index was 4 and the Wassermann reaction negative.

Progress. The patient remained under our care for three months. During most of this time he received proteolysed liver in daily doses of 1½ oz., but it will be seen from Fig. 6 that on no occasion was there evidence of a haematopoietic response. Throughout the period of observation blood platelets were scanty and purpuric bleeding from the gums and nose accounted for

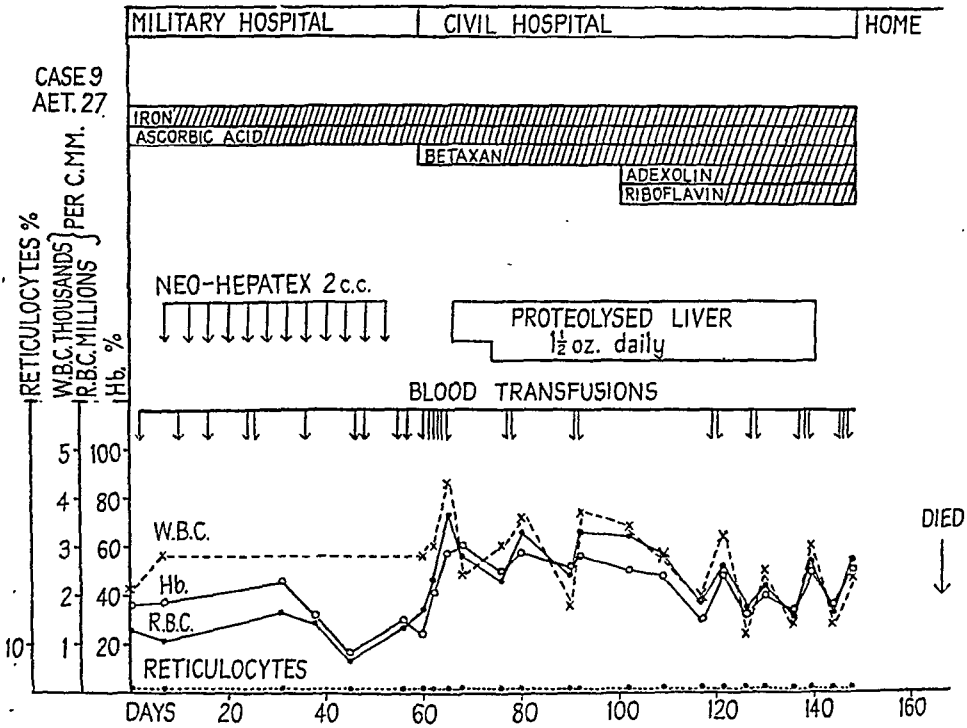

FIG. 6. Case 9, idiopathic hypoplastic anaemia in a young man; failure of haematopoietic response to proteolysed liver

much loss of blood, necessitating frequent blood-transfusions for the maintenance of life.

Discussion

Macrocytic anaemias associated with megaloblastic erythropoiesis are generally held to result from a deficiency of the anti-anaemic principle of Castle. This deficiency in turn may depend upon a lack of the extrinsic factor, as in tropical nutritional macrocytic anaemias, or defective production of the intrinsic factor as in Addisonian pernicious anaemia. Megaloblastic anaemia of pregnancy has been attributed to a combination of these causes aggravated by the demands of the foetus. Deficiency may also result from defective absorption of the elaborated anti-anaemic principle due to alimentary disorders such as sprue, steatorrhoea, and coeliac disease, or from interference with storage in the liver resulting from diseases of that organ. While these views provide a satisfactory explanation of the great majority of megaloblastic anaemias, there are undoubtedly lacunae in our knowledge of the pathogenesis of certain examples met with in practice. Thus, with

the possible exception of Case 5, the pathogenesis of the cases described in the present paper cannot with conviction be attributed to any one of the factors mentioned above.

It will be recalled that Israëls and Wilkinson (1936) have described cases of so-called 'achrestic anaemia' which differed from Addisonian pernicious anaemia in that free hydrochloric acid was present in the gastric juice and that treatment with liver extracts was ineffective. Failure in utilization or mobilization of the liver principle was postulated as the cause of these anaemias. Presumably our cases Nos. 2, 3, and 4 may be included in this category.

Consideration of the data presented in the present paper concerning the therapeutic value of proteolysed liver obviously renders it necessary to attempt to answer the question whether this substance was in fact superior to the parenteral liver extract with which it was compared. We believe the answer to be in the affirmative, but in asserting this belief it is necessary to dispose of a pertinent objection. This is based on our own earlier observations (Davidson, Davis, and Innes, 1942*a*, 1943) that certain cases of megaloblastic anaemia refractory to ordinary doses of parenteral liver extract did eventually respond to prolonged and massive dosage with the same extracts. Accordingly it might be argued that the recoveries of megaloblastic cases described here were due to the cumulative effect of the antecedent injections of liver extract together with the proteolysed liver and that the effect of the proteolysed liver itself was no more than would have occurred had the injections been persisted with. We believe that this argument is invalidated by the fact that the response to proteolysed liver was invariably immediate and vigorous. The objection could therefore be sustained only by postulating a series of coincidences which we consider too improbable to merit serious consideration.

In seeking a reason for the apparent superiority of proteolysed liver in the treatment of refractory megaloblastic anaemias two possible explanations present themselves. Firstly, it is conceivable that the refractory anaemias under consideration differed from classical pernicious anaemia simply in requiring a relatively greater quantity of haematopoietic principle for the restoration of red-cell maturation, and that the superiority of proteolysed liver therapy resulted from the assimilation of a greater quantity of the haematopoietic substance administered. Such a view is difficult to accept since it has repeatedly been shown that the active haematopoietic principle of liver is 60 to 100 times as effective when given by injection as by mouth (Castle, 1942). Moreover, the dosage of liver extract received by our cases was considerably greater than that necessary to produce a satisfactory response in cases of pernicious anaemia.

The second, and in our opinion the more likely explanation, is that proteolysed liver contains some factor of haematopoietic value lacking, or present only in inadequate quantities, in fractionated liver extracts. In this connexion it should be remembered that suggestive evidence has been reported

in the literature that raw liver may be more effective than liver extracts in the treatment of certain types of macrocytic anaemia (Davidson, 1939; Fullerton, 1943). Since proteolysed liver probably contains in a pre-digested form all the constituents of raw liver with the exception of fat, it is reasonable to assume that it also has the same therapeutic properties. It is probable, moreover, that the haematopoietic factors in proteolysed liver are more readily assimilable since it is effective in such relatively small doses in terms of whole liver. It should be noted that we have observed an adequate haematopoietic response in cases of pernicious anaemia with a daily dose of $\frac{1}{4}$ oz. which is derived from only $1\frac{1}{2}$ oz. of raw liver (Davis, Davidson, Riding, and Shaw, 1943).

The extremely prompt and effective response to proteolysed liver seen in our cases renders it tempting to speculate that the previous injections of liver extract had resulted in the erythropoietic tissues becoming fully charged, so to speak, awaiting only the advent of some additional factor for maturation to proceed apace. The calculated average rise in the blood count during the first 14 days of treatment with proteolysed liver in the five cases described above was approximately 1,400,000 red cells per c.mm., and 26 per cent. haemoglobin. It is also significant that in the three cases (Nos. 1, 3, and 4) in which sternal puncture was performed subsequent to numerous injections of liver extract, but before proteolysed liver was given, the marrow picture was morphologically indistinguishable from that seen before commencement of any form of treatment.

We suggest as a provisional hypothesis that while failure of maturation of the megaloblasts in the great majority of megaloblastic anaemias is due to a deficiency of the liver principle of Castle present in fractionated liver extracts, in refractory megaloblastic anaemias it results from an additional deficiency consequent on a failure in production or absorption of some other unknown factor which is present in adequate amount and assimilable form in proteolysed liver, and presumably also in whole liver. It should of course be understood that according to this view the therapeutic effect of the unknown factor in refractory megaloblastic anaemias is contingent upon an adequate quantity of the anti-anaemic principle of Castle also being made available. We believe that proteolysed liver is of peculiar value in that it is a convenient means of supplying both factors.

We have no data to present concerning the identity of the hypothetical additional factor, but the investigation of this problem is at present engaging our attention. It may not be out of place, however, to consider the possible nature of this factor. It is extremely unlikely that the factor is a mineral, since the content of proteolysed liver in iron and copper is respectively only 0·04 and 0·003 per cent. The possible effect of some trace element that may be present in a relatively high concentration should perhaps be considered.

The total protein content of proteolysed liver is approximately 70 per cent., but in view of the low dosage employed it is scarcely conceivable that this can be an adequate explanation of the haematinic virtue of proteolysed

liver. Conceivably the efficacy of proteolysed liver may lie in its content of certain amino-acids. In this connexion it should be noted that it contains methionine in a concentration of 1 per cent. The presence of this amino-acid is of possible significance in view of its importance in the cellular physiology of the liver. Bomford and Rhoads (1941) have adduced evidence suggesting that hepatic dysfunction may be an aetiological factor in refractory anaemias.

The vitamin content of proteolysed liver obviously requires consideration. Although whole liver is rich in vitamin A, proteolysed liver is deficient in the fat-soluble vitamins since they are lost during the process of its preparation. We are unaware of the concentration in proteolysed liver of ascorbic acid, aneurin, and nicotinic acid, but even if these vitamins are present in amounts equivalent to their concentration in whole liver, it is improbable, for reasons which have already been discussed, that they can be identified with the haematinic factor under consideration. We wish to emphasize in this connexion that our previous experience with refractory anaemias provided no grounds for assuming that the vitamins mentioned, even when given in very large doses along with injections of liver extract, exert any haematopoietic effect at all comparable in promptness or degree with that attributable to proteolysed liver. Proteolysed liver is rich in riboflavin (10 mg. per 100 gm.), but the influence of this vitamin on erythropoiesis is obscure. It may be noted that we have recently observed a remarkable clinical and haematological recovery following the administration of riboflavin in large doses in a case of sprue with megaloblastic anaemia which had long been refractory to treatment with liver extracts and liberal supplements of minerals and vitamins (excluding riboflavin). In other similar cases, however, the adminstration of riboflavin in large doses has been ineffectual. Attention has recently been drawn to the haematopoietic activity of folic acid (Axelrod, Gross, Bosse, and Swingle, 1943) which is contained in whole liver, but we have at present no data concerning its concentration in proteolysed liver. Biotin is also present in a relatively high concentration in liver and its deficiency in human beings has been shown to result in anaemia (Sydenstricker, Singal, Briggs, DeVaughn, and Isbell, 1942), but the therapeutic action of this substance in cases of refractory anaemia remains to be determined.

We have at present no satisfactory explanation to offer concerning the three cases of refractory anaemia with 'dimorphic' sternal marrows in which partial blood regeneration followed the administration of proteolysed liver. The morphology of the marrow films in these cases resembled that seen in cases of Addisonian pernicious anaemia 24 hours or so after the injection of liver extract (Davidson, Davis, and Innes, 1942*b*). Since these patients had all received numerous injections of liver extract prior to examination of the sternal marrow it is tempting to speculate that this may have resulted in a modification of the marrow morphology from a pre-existing frankly megaloblastic appearance. The incomplete conversion to normoblastic erythro-

poiesis and the inadequate blood regeneration might be attributed to the absence of some haematopoietic factor additional to that available in the liver extract. The objection to this hypothesis is that in the group of cases with frankly megaloblastic marrows, no modification in marrow morphology was observed after the injection of liver extracts. Furthermore, the administration of proteolysed liver to the cases in the 'dimorphic' group did not result in a haematopoietic response comparable in promptness or degree with that observed in the megaloblastic group. Consequently it is necessary to postulate that the abnormal erythropoiesis of the 'dimorphic' cases results from some intrinsic or extrinsic deficiency which is capable of only partial correction by whatever haematopoietic factors are available in proteolysed liver.

The failure of response to proteolysed liver of cases of anaemia with hypocellular normoblastic marrows may be explained by the concept that these anaemias are due to hypoplasia or atrophy of the haematopoietic tissue rather than failure of maturation. While it is of course quite unknown whether such hypoplasia is ever due to lack of a metabolic factor, there is no evidence for the existence of such a factor in liver or any other source. Any form of known haematinic treatment is accordingly ineffectual in cases of idiopathic origin, although of course in cases resulting from exposure to haemotoxic agencies where further exposure is averted before irremediable damage to the bone marrow occurs, energetic haematinic therapy is called for.

It should be noted that while drawing attention to the value of proteolysed liver in the treatment of certain types of refractory anaemia, we make no claim that equally good results could not have been obtained with whole liver or possibly with certain crude liver extracts, since no comparative trials with such substances were made by us. Carefully controlled trials in which the comparative merits of raw liver, proteolysed liver, and crude liver extracts are assessed in the treatment of anaemias refractory to refined liver extracts are obviously desirable. In practice, unfortunately, such trials are often impracticable since in severely anaemic patients delay in the institution of effective treatment may endanger life.

While we are of the opinion that whole liver in cases where it could be taken in adequate quantities might well prove as effective as proteolysed liver, we feel extremely doubtful whether the administration of so-called crude liver extracts would be of comparable therapeutic value. This view arises from the following considerations. Although it has been stated by a number of workers that so-called crude commercial liver extracts are more effective in some cases than more highly purified extracts in the treatment of macrocytic anaemias attributable to defective nutrition or to pregnancy, examination of published reports reveals a striking lack of unanimity. Thus, Wills and Evans (1938), Napier (1938), and Miller and Studdert (1938) reported that certain cases were refractory to 'Anahaemin' but responded to 'Campolon'. On the other hand Foy and Kondi (1939) in Macedonia, and Mudalier and Menon (1942) in India, found 'Anahaemin' and other

highly purified extracts to be as effective as 'Campolon' and other crude extracts in the treatment of large series of cases. In our own experience of the macrocytic anaemia of sprue, we have failed to obtain successful results with crude parenteral extracts in cases which were refractory to potent refined extracts. Furthermore, it should be mentioned that in a case of refractory megaloblastic anaemia of childhood to be described elsewhere (Davis, 1944) proteolysed liver therapy effected a prompt recovery, but subsequent maintenance treatment with injections of the crude liver extract 'Plexan' resulted in a deterioration of the blood picture. Resumption of proteolysed liver, however, was followed by restoration of a normal blood level. Finally it is noteworthy that in cases of macrocytic anaemias reported to be refractory to 'Anahaemin' but responsive to 'Campolon' or other crude extracts (Wills and Evans, 1938), the responses obtained were moderate in degree compared with the vigorous responses to proteolysed liver noted in the megaloblastic anaemias described by us.

In conclusion we wish it to be understood that we do not advocate proteolysed liver for the routine treatment of Addisonian pernicious anaemia, since in uncomplicated cases of this condition injections of potent liver extract are highly effective and provide the most economical form of treatment. In our opinion proteolysed liver should be reserved for cases refractory to parenteral treatment.

Summary

1. An account has been given of the response to oral proteolysed liver in 13 cases of severe anaemia which had proved refractory to treatment with injections of liver extracts of known potency.

2. In five of the cases the morphology of the peripheral blood and sternal marrow was respectively macrocytic and megaloblastic and were typical of Addisonian pernicious anaemia, although only one of the cases conformed fully in other respects to the usual diagnostic criteria for this disease.

In all these cases the administration of proteolysed liver resulted in a prompt and vigorous haematopoietic response and the rapid restoration of the patient to normal health.

3. In three other cases the anaemia was also macrocytic, but the sternal marrow films showed 'dimorphic' erythropoiesis. Proteolysed liver in these cases was followed by only partial blood regeneration with the survival of the patients in moderate health.

4. The remaining five cases of anaemia were of the aplastic type with hypocellular normoblastic sternal marrow, and completely failed to respond to proteolysed liver or to any other form of treatment.

5. The significance of these observations is discussed and it is suggested that proteolysed liver contains, in a readily assimilable form, some haematopoietic maturation factor additional to the anti-anaemic factor present in fractionated liver extracts.

We wish to record our gratitude to Professor W. T. Ritchie, Professor D. M. Dunlop, and Dr. W. A. Alexander, for allowing us to study patients under their care. We are also indebted to Dr. D. Riding of Messrs. Evans, Lescher, and Webb, for generous supplies of proteolysed liver.

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A CRITICAL REVIEW OF PERNICIOUS ANAEMIA OF PREGNANCY[1]

By Sheila T. E. Callender

(From the Nuffield Department of Clinical Medicine, Oxford)

With Plates 3 to 8

Introduction

The association of anaemia with pregnancy is well recognized. In this country the anaemia is commonly due to iron deficiency and is hypochromic. In the tropics a macrocytic hyperchromic anaemia of pregnancy has attracted attention and has been the subject of many recent investigations. Its counterpart in temperate climates, the so-called pernicious anaemia of pregnancy, has been considered extremely rare and therefore of little practical significance. It was first recognized over a century ago when Channing in America encountered 10 fatal cases of severe anaemia associated with pregnancy. These he reported in his 'Notes on Anhaemia, principally in its connexions with the Puerperal State and with Functional Diseases of the Uterus' (Channing, 1842). Three similar cases were published by Lebert in 1854 from the canton of Zürich, and 17 years later Gusserow (1871) reported five fatal cases of '*Höchgradigste Anämie Schwangerer*' which had occurred in his clinic between 1868 and 1870.

Biermer's original description of 'progressive pernicious anaemia' (Biermer, 1872) included cases which dated from confinement. Ehrlich and Lazarus (1898), in describing pernicious anaemia, commented on cases occurring in association with pregnancy. They grouped them separately on grounds of aetiology, but made no haematological distinction. It was not until 1919 that Osler drew attention in this country to a severe anaemia of pregnancy which he distinguished from Addisonian anaemia only by the frequency of recovery and the absence of recurrence (Osler, 1919). At this time his experience was quite exceptional as the previously reported cases had nearly all been fatal. Until recently the blood picture was generally accepted as being indistinguishable from that of true pernicious anaemia and little heed was paid to isolated descriptions of atypical findings. The response to liver therapy first reported in 1928 (Brault, 1928; Audebert and Fabre, 1928; Devraigne and Laennec, 1928) demonstrated a further similarity between pernicious anaemia of pregnancy and Addisonian anaemia. Although Filo (1931) commented on the fact that achylia was not the rule as in true pernicious anaemia, he did not see the necessity for distinguishing the two

[1] Received June 2, 1944.

conditions. Naegeli (1931, 1935) was also of this opinion. Within the last 10 years, however, evidence has gradually been accumulating which makes it clear that this view can no longer be held. Studies of larger numbers of cases than had hitherto been reported and the use of sternal puncture in diagnosis have shown that the blood picture may lack many of the characteristic features of Addisonian anaemia (Stevenson, 1936, 1938; Abramson, 1938; Segerdahl, 1941; Miller and Studdert, 1942; Davidson, Davis, and Innes, 1942*b*; Lescher, 1942). Furthermore, attention has been drawn to the fact that some patients are temporarily refractory to treatment with liver extracts, which are potent in true pernicious anaemia (Ungley, 1938; Ritter and Crocker, 1939; Nielsen, 1941; Davidson, Davis, and Innes, 1942*b*; Fullerton, 1943).

Although the total number of previous case reports is large, many of the earlier records are of limited value. The haematological data are often scanty or vague, and in some instances an alternative diagnosis of iron-deficiency anaemia, post-haemorrhagic anaemia, or anaemia due to infection cannot be excluded on the available evidence. The general conception of the illness has therefore been confused. Some 255 of the previous reports may be accepted as probable cases of pernicious anaemia of pregnancy, though in considerably less than half of this number was the diagnosis proven. The present review is based in addition on 25 cases which I have observed personally and in which the diagnosis was established beyond doubt.

Two particular features were taken to be diagnostic of this anaemia, namely, the presence of true megaloblasts[2] in the peripheral blood and the demonstration of a megaloblastic change in the bone-marrow. I have relied heavily on these personal cases for descriptions of the morbid anatomy of the disease and cytology of the bone marrow, which are not adequately described in the literature.

General Features

Pernicious anaemia of pregnancy occurs at any age during the child-bearing period of life in both primigravidae and multigravidae. Although the majority of patients live in poor economic circumstances and have a defective diet, a few exceptions have been noted (Stevenson, 1938; Segerdahl, 1941; Miller and Studdert, 1942; Nos. 5, 7, 8, and 25 of the present series). A previous history of anaemia or ill health is not unduly frequent, and only three instances of a family history of anaemia have been recorded. Schmidt (1918) described a patient whose mother was said to have died of pernicious anaemia of pregnancy; the sister of one of Miller and Studdert's (1942) patients and the mother of one of my patients (No. 12) had Addison's anaemia.

The time of onset of the anaemia is difficult to assess, for it is rare for the patient to come under supervision before the illness is well established.

[2] The term megaloblast is used throughout as defined by Naegeli and his school, that is, to denote a cell which is found only in conditions of liver factor deficiency and which does not represent a stage in normal erythropoiesis.

Most commonly symptoms arise during the third trimester or in the puerperium, but occasionally they have dated from early pregnancy or a miscarriage (Naegeli, 1912; Osler, 1919; Vermelin and Vigneul, 1921; Drexel, 1926; Pohl, 1928; Batisweiler, 1933; Ionescu and Bonciu, 1935; Stevenson, 1938; Onhauser and Mitchell, 1939; Lescher, 1942).

The rapidity of onset may be striking, as in one patient of my series in whom the haemoglobin value fell from 64 to 39 per cent. in the last 12 days

TABLE I

Incidence of Sepsis in 41 Patients with Pernicious Anaemia of Pregnancy

Type of infection	Number of patients C	Number of patients D	Combined series
Mastitis	4	4	8
Pyelitis	7	3	10
Pneumonia	–	2	2
Endometritis and/or cervicitis	4	–	4
Suppurating glands of neck	1	–	1
Thrombophlebitis	1	–	1
No infection	8	7	15

C = Personal observations. D = Series of Davidson, Davis, and Innes (1942*b*).

of pregnancy; on the other hand, it may be so insidious that the condition is not recognized until many months after confinement (Larrabee, 1925; Stevenson, 1938; Nos. 9, 19, 20 (ii), and 24 of the present series).

Apart from the general symptoms common to all severe anaemias, gastrointestinal complaints are prominent. Either excessive vomiting or diarrhoea is a feature in 40 to 50 per cent. of cases. The patients may also complain of a sore tongue, and glossitis and atrophy of the papillae have been described (Naegeli, 1931; Abramson, 1938; Segerdahl, 1941; Miller and Studdert, 1942; Fullerton, 1943; Nos. 3, 8, and 20 of the present series), but the tongue changes are not as constantly seen as in Addison's anaemia. While slight oedema is of common occurrence, massive oedema is also sometimes seen. In some women this has been attributable to accompanying pre-eclamptic toxaemia, but Naegeli (1912) and Beckman (1921) each described a patient with generalized oedema and serous effusions, but only a trace of albumin in the urine. Two similar cases occurred in my series. In one of these malnutrition and hypoproteinaemia played a part. Patients have generally been described as showing a yellowish pallor, but in my series such an appearance was exceptional even where there was profound anaemia. The 'delicate pearly white appearance' referred to by Gallupe and O'Hara (1924) was far more characteristic.

The spleen is enlarged in about 30 per cent. of patients. It may be only just palpable or may extend three to four inches below the costal margin. Less frequently the liver is also enlarged. Gradual diminution in size accompanies clinical improvement. Purpuric eruptions or haemorrhages from mucous membranes are occasionally seen. Retinal haemorrhages have been found in nearly half of those patients in whom an ophthalmoscopic examination has been made (Stevenson, 1938; Miller and Studdert, 1942).

Although pyrexia is common, the association with sepsis has been said to be infrequent; for example, Stevenson (1938) noted pyrexia in 17 of her 30 patients, but in only one of these was sepsis demonstrated. Both my series and that reported by Davidson, Davis, and Innes (1942 *b*) offer a contrast in that septic complications occurred in 26 of the combined series of 41 patients (Table I). Pre-eclamptic toxaemia, and ante-partum and post-partum haemorrhage may occur as added complications, but there is no evidence that they are unduly frequent.

Blood Changes

The blood picture is remarkably variable. Among earlier reports the features most often described were those of a severe macrocytic hyperchromic anaemia indistinguishable from Addison's anaemia. Recently less characteristic findings have been recognized (Stevenson, 1938; Abramson, 1938; Segerdahl, 1941; Miller and Studdert, 1942; Davidson, Davis, and Innes, 1942 *b*; Lescher, 1942), and in my series they were not uncommon (Table II). Wintrobe (1942) states that the anaemia is usually less severe than in true pernicious anaemia, but this hardly seems to be the case, for the haemoglobin is frequently below 30 per cent. or even 20 per cent. by the time the diagnosis is made. Although the colour index is usually normal or raised, it may be below unity and in some instances, in which the diagnosis has been proved by marrow biopsy, it has been as low as 0·75 (Abramson, 1938; Davidson, Davis, and Innes, 1942 *b*). It was 0·9 or under in five of my series.

Heilbrun (1936), Doan (1938), Ungley (1938), and Miller and Studdert (1942) all record high values for the mean corpuscular volume (M.C.V.) ranging between 96·7 μ^3 and 157 μ^3, but Naegeli (1931) described a single patient with an M.C.V. of 93 μ^3, and four of the 12 estimations made in my series came within the normal range of 75·744 μ^3 to 96·096 μ^3 (Price-Jones, Vaughan, and Goddard, 1935), the lowest value being 80·2 μ^3. Minot's patient with an M.C.V. of 67·7 μ^3 presented several unusual features, and in the absence of a marrow biopsy the diagnosis of pernicious anaemia of pregnancy can hardly be taken as proved (Minot, 1921).

Records of Price-Jones curves reflect the variations in the blood picture. Hampson and Shackle (1924) reported one case with a curve typical of Addison's anaemia. Similar curves have been found by Stevenson (1938) in six of her 30 patients, by Ungley (1938) in one of his six, and in four of the present series (Fig. 1). More commonly the mean diameter is normal though the base of the curve is widened (Stevenson, 1938; Ungley, 1938; Segerdahl, 1941). Even in severe cases a curve may be found which approaches closely to the normal, and megalocytosis may be entirely absent (Fig. 2).

The figures recorded for the mean cell diameter (M.C.D.) as measured by Price-Jones's method give a range of 6·89 μ to 8·98 μ. In the majority of instances the mean diameter is within the normal limits of 6·686 μ to 7·718 μ (Price-Jones, Vaughan, and Goddard, 1935), and it is frequently below

7·546 μ, the figure which Price-Jones (1933) considered suspicious of true pernicious anaemia. In Segerdahl's (1941) two patients, and in six of my series, in all of whom the diagnosis was confirmed by sternal puncture, the M.C.D. was less than the normal mean of 7·2 μ.

An increased fragility of the red cells was found by a few observers (Minot, 1921; Vallois and Coll de Carréra, 1923; Vermelin and Vigneul, 1921; Devraigne and Laennec, 1928; Lenner, 1930) in supposed examples of pernicious anaemia of pregnancy, but others have failed to confirm this (Filo, 1931; Swan, 1933; Stevenson, 1938; Nielsen, 1941). Miller and Studdert (1942) found only an insignificant increase in three out of nine cases tested, and in three of my series the mean corpuscular fragility was either normal or diminished, even after correction for anaemia.

TABLE II

Blood Findings in the Present Series at the Time of Diagnosis, Arranged in Order of M.C.D.

Case	Hb. %	C.I.	M.C.H.C. %	M.C.V. μ^3	M.C.D. μ	σ μ	v %	W.B.C. per c.mm.
11	48	1·2	—	—	6·92	0·578	8·36	4,400
18	39	1·0	33·6	80·2	6·97	0·547	7·85	3,100
21 (ii)	46	1·1	33·4	90·0	7·06	0·576	8·16	5,600
13	18	0·78	—	—	7·08	0·968	13·68	3,600
15	36	1·2	—	—	7·15	0·626	8·75	3,600
12	41	0·76	—	—	7·17	0·695	9·69	11,500
21 (i)	18	1·06	—	—	7·20	0·776	10·77	2,250
5	30	0·9	28·7	101·6	7·20	0·702	9·75	5,000
22	16	1·4	—	—	7·35	0·917	12·47	2,400
20 (i)	26	1·0	—	—	7·40	0·965	13·04	11,500
6	44	1·3	36·8	97·06	7·46	0·803	10·76	8,200
14	36	1·0	—	—	7·49	0·712	9·50	4,000
1	20	1·2	—	—	7·53	1·035	13·75	9,200
16	20	0·9	—	—	7·55	0·782	10·35	9,800
25	30	1·0	25·9	106·7	7·57	0·852	11·24	12,800
4	20	1·3	34·5	109·6	7·66	1·11	14·50	2,062
10	54	1·03	32·4	88·1	7·68	0·775	10·09	9,150
3	24	1·37	31·4	120·7	7·71	1·233	15·99	3,200
8	48	1·1	33·1	92·6	7·72	0·621	8·04	9,400
17	13·5	1·1	—	—	7·73	1·15	14·88	6,400
9	32	1·15	32·7	97·8	7·89	0·738	9·36	1,900
20 (ii)	44	1·37	—	—	8·03	0·734	9·15	6,200
19	38	1·26	30·84	113·3	8·06	1·287	15·97	4,800
7	20	1·2	27·6	117·6	8·61	0·717	8·33	5,800
2	22	0·85	—	—	—	—	—	6,000

Figures for patients 20 and 21 are given for two successive pregnancies. No counts are available for patients 23 and 24.

Elliot (1944) has shown that a tendency to anisocytosis may be a normal finding in healthy pregnant women. The coefficient of variation (v) and the standard deviation (σ) in his series of 14 women were 6·6 to 9·2 per cent. and 0·466 to 0·708 μ. The values previously recorded in cases of pernicious anaemia of pregnancy have all been outside this range, v varying from 11·36 to 17·7 per cent. and σ from 0·8 to 1·59 μ. In my series, however, seven of the figures for v and for σ were below 9·2 per cent. and 0·708 μ respectively, although they were above Price-Jones's standard of normal

(v 5·3 to 7·3 per cent.; σ 0·4 to 0·5μ). The lowest value for v was 7·85 per cent. and for σ 0·547μ.

In the blood-films the cells may appear normal in size and shape with uniform staining. At the other extreme, anisocytosis and poikilocytosis are

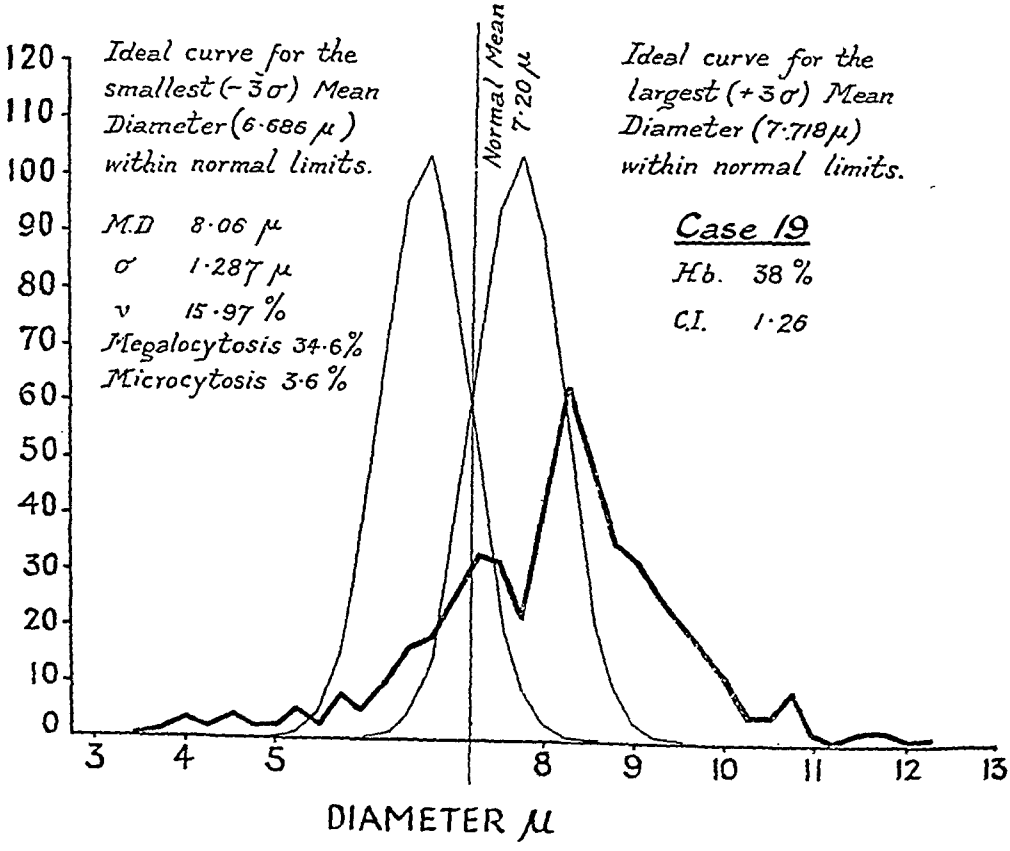

FIG. 1. Price-Jones curve from a patient in whom anaemia dated from her delivery four months before (Case 19)

obvious features, and ovalocytosis has also sometimes been noted. Nucleated red cells of both the normoblastic and megaloblastic series are often found in the peripheral blood-films, although an extensive search may be required before they are discovered. Typically they are fully haemoglobinized Ehrlich megaloblasts, but occasionally more basophilic forms are found (Plates 6 and 7, Figs. 10 to 16). Nucleated red cells in mitosis may also be seen. A low reticulocyte count is usual in the untreated cases, but in some instances the reticulocyte count has been high even before treatment has been instituted. Lescher (1942) in his series separates the latter group from his patients with low reticulocyte counts, and classifies them as haemolytic anaemias.

White-cell counts have ranged from about 1,000 to 12,000 per c.mm., with occasional higher values up to 45,000 per c.mm. When compared with the physiological leucocytosis which frequently, though not invariably, occurs during pregnancy and the puerperium (Carey and Litzenberg, 1936;

Gibson, 1937; Whitby and Britton, 1942), a pathological leucocytosis is only rarely found. On the other hand, a true leucopenia is common, the granular cells being principally affected (Table II). In the blood-films a few myelocytes and young forms are nearly always present and occasionally the

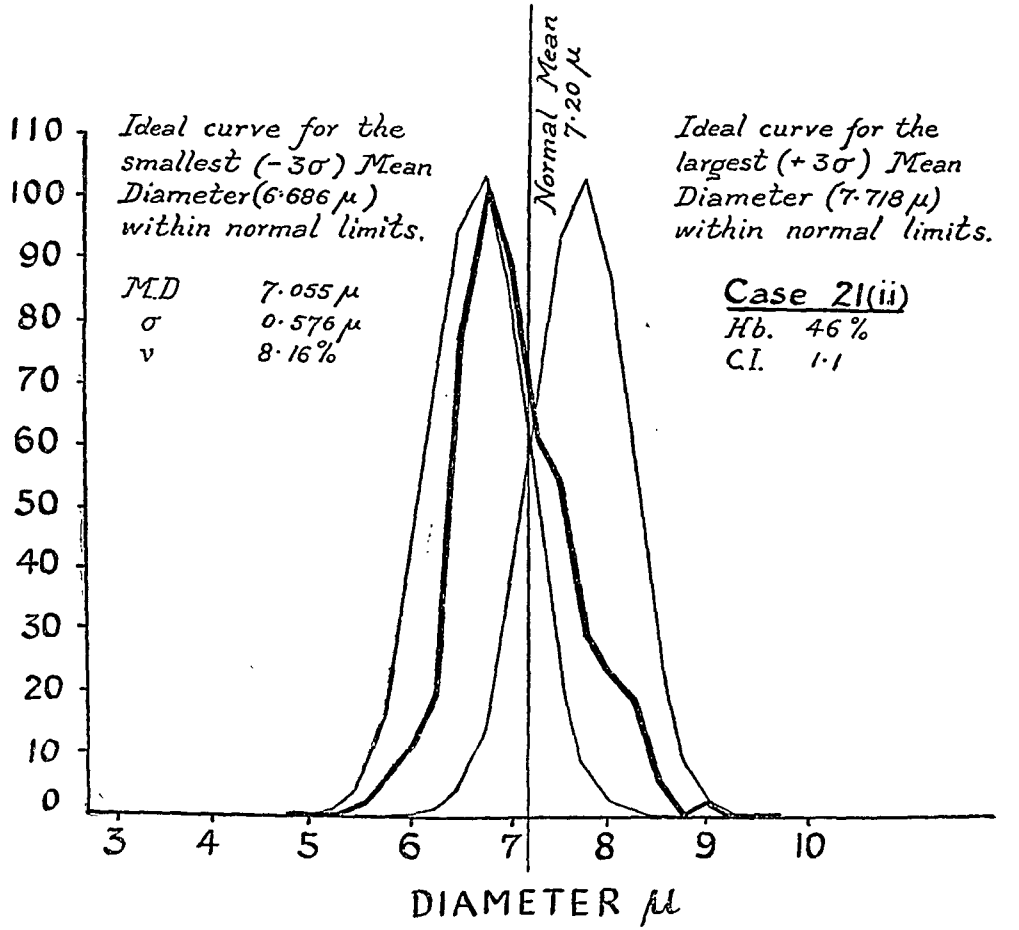

FIG. 2. Price-Jones curve from a patient seven and a half months pregnant. Duration of anaemia about one month (Case 21 (ii))

macropolycytes and hypersegmented forms characteristic of Addison's anaemia may be seen.

It is difficult to judge the frequency of thrombocytopenia from the few available observations. The figure was less than 200,000 per c.mm. in five of the six counts in my series, and Filo (1931) found thrombocytopenia in all his five patients. On the other hand, two out of four of Abramson's (1938) counts were normal and Stevenson (1938) considered that the platelets were fairly numerous as a rule.

Biochemical Investigations

Some reports indicate that a slight rise in the plasma-bilirubin may accompany the anaemia (Peterson, Field, and Morgan, 1930; Filo, 1931;

Heilbrun, 1936; Abramson, 1938; Stevenson, 1938), but of the 11 patients in my series on whom the estimation was made, none showed a value higher than 0·8 mg. per 100 c.c., and in nine the value was 0·4 mg. or less. The plasma-iron or serum-iron has been determined in only four instances (Doan, 1938; Segerdahl, 1941; Nos. 7 and 8 of the present series). Before treatment the values were 95, 165, 190, and 270 micrograms per 100 c.c. A rapid fall occurred with the reticulocyte response. In contrast to Addisonian anaemia, achlorhydria is not the rule. Among 121 records of gastric analyses only 34 women have had complete achlorhydria, and some of these may not have been histamine fast. One of my patients showed a response only after histamine. Six women with achlorhydria were re-examined after recovery from the anaemia and showed a return of normal secretion (Batisweiler, 1933; Strauss and Castle, 1933; Ungley, 1938; Lescher, 1942; No. 21 of the present series).

Bone-Marrow

The first description of bone-marrow biopsy in pernicious anaemia of pregnancy was given by Heilbrun (1936), who obtained marrow by sternal trephine and prepared both smears and sections. Several other studies have been made, but few detailed descriptions have been given in the reports (Daniachij, 1936 *b*; Doan, 1938; Markoff, 1939; Rohr, 1940; Nielsen, 1941; Segerdahl, 1941; Davidson, Davis, and Innes, 1942 *b*; Miller and Studdert, 1942; Lescher, 1942; Fullerton, 1943). Marrow was obtained by sternal puncture in 12 of my series, in some women both before and after treatment (Table III). While the blood picture may be atypical, the marrow changes before treatment are in general similar to those described in Addisonian anaemia (Tempka and Braun, 1932; Segerdahl, 1935; Dameshek and Valentine, 1937; Schulten, 1937; Jones, 1938; Scott, 1939; Rohr, 1940) (Plates 3 and 5, Figs. 3, 4, and 8). In the majority of cases there is a mixed megaloblastic and normoblastic reaction with the formation of characteristic clumps of deeply basophilic promegaloblasts and megaloblasts. Multinuclear megaloblasts and giant forms are not uncommon, and the degenerate cells described by Segerdahl (1935, 1941) with a coarse reticulate and sometimes irregularly lobed nucleus may be seen. Leucopoiesis is sometimes strikingly predominant, the leuco-erythrogenic ratio being more than 3 : 1. In one of my patients (No. 18) it was as much as 4·49 : 1. The pathological white-cells showing vacuoles, peculiar invaginations of the nuclei, and discrepancy between nuclear and cytoplasmic development are also found, many of them being giant forms (Plates 5 and 7, Figs. 8 and 18). No particularly characteristic changes in the megakaryocytes have been observed. In two of my series they were plentiful and well preserved, some being primitive with basophilic cytoplasm and scanty azurophil granulation. In the others they appeared to be reduced in number.

Rohr (1940) and Segerdahl (1941) are the only observers who have attempted to distinguish the marrow changes from those of true pernicious

TABLE III

Differential Counts on Sternal Marrow Films

Case	(8)		(21)		(5)		(7)		(18)	(25)	(3)	(4)	(6)	(10)	(9)	(19)
	i	ii	i	ii	i	ii	i	ii								
Haemocytoblast	—	—	0·4	0·8	0·8	1·0	0·5	—	0·2	2·2	0·75	0·5	—	0·5	0·75	2·0
Promegaloblast	—	1·25	3·8	—	1·6	—	0·75	—	0·4	1·2	1·75	1·0	1·0	0·5	1·75	—
Megaloblast — Basophil	—	3·25	3·2	—	16·8	—	6·0	—	2·8	10·6	6·0	4·0	11·5	0·5	4·5	1·0
Megaloblast — Polychromatic	—	3·75	8·6	—	8·4	—	3·75	—	6·8	4·4	7·75	7·25	12·0	1·0	1·5	7·25
Megaloblast — Orthochromatic	—	1·0	1·6	—	1·6	—	1·0	—	2·6	2·8	5·0	1·25	5·75	0·5	0·5	1·5
Pro-erythroblasts	0·25	0·75	—	—	1·2	0·5	—	0·5	—	0·4	0·75	0·5	0·25	0·5	2·0	2·25
Erythroblast — Basophil	1·25	4·25	—	9·2	2·0	1·0	4·0	1·25	—	5·2	1·25	3·5	3·5	4·25	5·25	18·0
Erythroblast — Polychromatic	9·0	5·5	—	16·4	0·4	29·25	0·75	16·25	0·4	1·6	4·5	6·5	5·25	10·75	2·0	25·75
Erythroblast — Orthochromatic	3·0	3·0	1·0	10·0	0·8	6·25	0·75	7·75	0·6	2·4	7·5	3·5	10·25	10·75	2·75	6·0
Myeloblasts	1·75	3·25	3·0	—	2·8	1·0	1·0	2·25	1·4	1·6	1·25	2·25	1·25	2·0	3·25	2·5
Promyelocytes	3·0	6·5	3·6	0·8	0·8	—	8·5	2·25	7·6	2·6	1·75	5·5	1·25	2·0	5·5	0·75
Neutrophil — Myelocyte	16·5	18·25	21·6	16·0	20·0	16·0	24·25	14·75	25·4	24·4	15·25	23·25	9·25	20·5	31·0	11·5
Neutrophil — Young	11·25	15·25	19·0	16·4	17·2	6·5	19·5	16·0	20·2	15·2	13·5	16·25	11·75	15·5	17·25	8·25
Neutrophil — Band	12·0	15·0	14·0	9·6	6·4	14·5	16·0	14·25	9·2	5·6	11·5	5·75	7·75	12·5	12·0	4·0
Neutrophil — Segmented	19·0	9·5	7·4	10·4	9·2	4·0	3·5	7·0	5·2	9·6	8·25	5·0	7·5	8·25	2·25	2·0
Eosinophils	4·5	1·75	4·4	2·8	0·8	7·5	1·75	5·5	2·6	1·2	2·0	3·75	2·75	3·0	1·25	1·0
Basophils	—	—	—	—	—	1·0	—	0·75	—	0·2	—	0·25	0·25	—	—	—
Lymphocytes	10·75	3·5	5·4	4·0	6·8	7·0	6·0	9·5	12·0	5·6	9·0	5·0	5·0	3·0	4·0	2·25
Monocytes	5·75	0·25	1·2	2·4	0·8	—	—	1·0	0·8	—	0·5	0·25	0·5	0·5	—	0·25
Plasma and reticulum cells	1·25	2·25	0·6	0·8	0·4	1·0	1·5	0·5	1·0	1·4	0·75	2·5	—	2·25	2·25	0·25
Megakaryocytes	0·25	0·25	0·2	—	—	—	—	—	—	—	—	—	—	0·25	0·25	—
Mitoses	0·5	1·5	1·0	0·4	1·2	3·5	0·5	0·5	0·6	1·2	0·5	1·5	2·5	1·0	—	4·25
Unclassified	—	—	—	—	—	—	—	—	0·2	0·6	0·5	0·75	0·75	—	—	—

Case 8 { i, during the sixth month of pregnancy.
ii, ten days after delivery.

In Cases 21, 5, and 7, i = before treatment, ii = after treatment.

Case 19, five days after starting liver treatment.

The rest untreated.

anaemia. They both found a more mature type of erythropoiesis than is usual in Addison's anaemia, with fewer promegaloblasts and basophilic megaloblasts and relatively more ripe forms. This was undoubtedly a feature of one of my patients in whom haemoglobinized megaloblasts and gigantoblasts were far more frequent than the earlier cell types (Plate 7, Fig. 17). One other woman also showed a scarcity of deeply basophilic red-cell precursors. This was not due to the fact that her marrow was more mature in type; on the contrary, primitive cells were abundant. A few of these were cells of indeterminate nature, possibly corresponding to those described by Rohr (1940) in true pernicious anaemia as large proliferated reticulum cells. For the purposes of classification they were termed 'haemocytoblasts'. Intermediate between these and early haemoglobinized megaloblasts there were cells measuring 25 to 30 μ in diameter, having a wide rim of light blue cytoplasm, a nucleus with fine reticulate structure and three or four nucleoli (Plate 3, Fig. 3*a*). These were undoubtedly red-cell precursors, as all transitions were seen between them and fully haemoglobinized megaloblasts. The more usual type of promegaloblast with intensely basophilic cytoplasm was relatively inconspicuous (Plate 3, Figs. 3 and 4). These two patients, although by no means the most gravely anaemic of my series, showed an almost exclusively megaloblastic type of erythropoiesis, a finding which is unusual in true pernicious anaemia (Jones, 1938). The few cells which were classed in the normal series were late polychromatic or orthochromatic cells with pyknotic nuclei which, as Ehrlich, Naegeli, and others have pointed out, might equally well be derived from the abnormal series. The majority of the red-cell precursors were gigantoblasts measuring up to 30 μ in diameter. These findings were all the more remarkable in that both women had a normocytic anaemia with a mean cell diameter to the left of the normal mean and a complete absence of megalocytosis (Fig. 2). A third patient was of particular interest. Her sternal marrow had been examined during the sixth month of pregnancy and found to be normal. During the last month anaemia developed and 10 days *post-partum* the marrow showed a typical megaloblastic change (Plate 5, Figs. 7 and 8).

In the majority of cases typical megaloblasts are easily found, but occasionally they are few in number and may be found only after a careful search. This was so in some of Segerdahl's (1941) patients, and in one of my patients in whom the clinical and haematological picture and the course of the illness suggested that a spontaneous remission was taking place.

In response to treatment the changes are identical with those seen in true pernicious anaemia (Tempka and Braun, 1932; Segerdahl, 1935; Schulten, 1937; Davidson, Davis, and Innes, 1942*a*). The megaloblastic character of the marrow rapidly disappears and there is a striking proliferation of macronormoblasts and normoblasts. Evidence of abnormal leucopoiesis seems to persist rather longer than the megaloblastic erythropoiesis (Plates 4 and 6, Figs. 5, 6, and 9).

Morbid Anatomy

No detailed necropsy reports have been found in the available literature. Some of the earlier papers give descriptions of the macroscopic post-mortem findings, the usual picture being one of profound anaemia with fatty change and haemosiderosis in the organs, associated with a hyperplastic bone-marrow and a tendency to capillary haemorrhages in the serous membranes (Esch, 1917; Beckman, 1921). Stevenson (1938) has given a little more detail in describing one necropsy. She found catarrhal changes in the gastric mucous membrane, a congested spleen, a fatty liver, and megaloblastic change in the bone-marrow, but no iron reaction in the organs. Onhauser and Mitchell (1939), on the other hand, comment on excessive pigment in the liver and spleen of their patient who died when only five months pregnant.

A post-mortem examination was held on all three fatal cases in my series. On naked-eye examination the noteworthy features were the extreme waxy pallor, which was entirely different from the lemon-yellow colour of true pernicious anaemia, the normal appearance of the gastric mucosa in every case, and the absence of any marked fatty change in the organs of one of the patients. In the other two the heart showed the 'thrush breast' appearance commonly found in true pernicious anaemia. The amount of iron in the organs was variable. In two of the women the liver and kidneys gave a well-marked Prussian blue reaction, whereas the spleen gave only a slight reaction. These organs in the third patient gave only a faint reaction. In all three the bone-marrow was hyperplastic and red marrow extended practically throughout the shaft of the femur with absorption of the bony trabeculae in the upper part of the marrow cavity.

Sections of the marrow from the femur show almost entire replacement of the fat cells by active haemopoietic tissue. The picture is essentially similar to that described by Peabody (1927) in Addisonian anaemia. Large clumps of extremely primitive cells with basophilic cytoplasm and a clear vesicular type of nucleus predominate (Plate 8, Figs. 20 and 21). It seems clear from comparison between smears obtained by sternal puncture and post-mortem material from one patient (No. 25) that Turnbull's (1936) use of the term 'haemocytoblast' to describe these cells is misleading. In the smear, while there are many basophilic cells, these are nearly all differentiated and can be classified as early erythroblasts of the normal and megaloblastic series. Whatever the nomenclature used, it seems almost certain that the clumps of very primitive cells seen in the sections are red-cell precursors. All stages of haemoglobinization may be observed, from the faintest trace of polychromasia in large cells with nuclei indistinguishable from those of the early basophilic cells, to fully haemoglobinized megaloblasts with pyknotic nuclei.

The proportion of normal erythropoiesis appears to be small in the marrow of two of the patients. The majority of the dark nuclei belong either to lymphocytes or pyknotic megaloblasts. In the third, on the other hand, the megaloblastic character is not so well developed and a fair proportion of

normoblastic erythropoiesis can be identified. In addition to the changes in erythropoiesis, the sections show a definite proliferation of myelocytes, giant forms being easily recognized. In two, eosinophil myelocytes are particularly numerous. Mature white cells are few in number. Erythrophagocytosis is a feature of all three, and mitotic figures are relatively frequent. In one, small clumps of plasma-cells occur, particularly round the blood-vessels. Sections stained with the Prussian blue reagents show that iron is present in the endothelial cells lining the capillaries in the marrow of one patient, and to a less extent in that of the second. Iron is also contained in a few macrophages. The pigment is almost entirely absent from the marrow of the third patient.

Foci of extramedullary haemopoiesis were found in all three women. In the sections of spleen the sinusoids contain very few mature red cells, but clumps of immature cells are not infrequent (Plate 8, Fig. 22). Here and there clusters of eight or more of the early megaloblasts observed in the marrow are found. These groups of primitive cells are practically entirely confined to the venous sinusoids and only occasional similar cells are found in the pulp. Later stages of erythropoiesis are not so conspicuous, but can be identified. Myelocytes are plentiful in the pulp, and in Nos. 23 and 24 eosinophils are particularly conspicuous. In the liver also foci of erythropoiesis are found. They occur within the sinusoids, particularly in the mid-zone of the lobules. In one they are composed of the primitive type of cell only, but in the other two a few more mature groups of nucleated red cells are also seen. No foci of haemopoiesis are present in the sections of the kidney.

The three patients differed considerably with regard to the degree of fatty change in the organs. In the sections of liver from one there is such pronounced fatty change at the centres of the lobules that the hepatic cells resemble those of adipose tissue. There is moderate fatty change in another, while in the third the liver cells show little alteration. Two of the three show well-marked fatty change in the kidney.

Sections of the liver from the first patient, when stained for iron show, as in true pernicious anaemia, a heavy deposit in the outer two-thirds of the lobules (Plate 7, Fig. 19). In the periportal zones the iron is chiefly contained in the hepatic cells, but nearer the centres of the lobules the Kupffer cells contain abundant iron in granular form. There is far less iron in the liver of the second patient, and in the sections from the third only occasional Kupffer cells contain granules of pigment, and the hepatic cells are free from deposit. In all three, however, the liver cells toward the centre of the lobules contain a small amount of golden-brown pigment which fails to give the iron reaction. In the spleen of the first patient the Prussian blue reaction reveals occasional clusters of macrophages containing iron both in the pulp and along the trabeculae, in addition to scattered reticulo-endothelial cells containing pigment. These are most frequent round the periphery of the Malpighian bodies. There is very little iron in the endothelial cells lining the venous

sinusoids, but those lining some of the smaller splenic veins contain a considerable amount of pigment. In sections of spleen from the other two only occasional reticulo-endothelial cells contain granules of iron. In the kidney there is considerable storage of iron, especially in the cells of the proximal tubules in two of the three cases.

The stomach was examined microscopically in only one patient. Superficially the cells are destroyed by post-mortem change, but the deeper parts of the glands are well preserved. There is no evidence of any inflammatory change, but the glands are reduced in size and are less complex in formation than normally.

Diagnosis

Pernicious anaemia of pregnancy is only one of the many types of severe anaemia which may occur during pregnancy and the puerperium, and the question of differential diagnosis may be far from easy. It has often been stressed that associated pyrexia may lead to the mistaken diagnosis of puerperal sepsis, or that oedema and albuminuria may suggest toxaemia or chronic nephritis. There is also no doubt that the reverse may be equally true, and that some of the cases reported as examples of pernicious anaemia of pregnancy were, in fact, only severe anaemias secondary to sepsis, toxaemia, or even iron deficiency or haemorrhage. Cabot (1927), for example, quotes a case in which the clinical diagnosis had been pernicious anaemia of pregnancy, but autopsy revealed an unsuspected diphtheritic endometritis. To add to the confusion in diagnosis, haemorrhage, sepsis, or pre-eclamptic toxaemia may all be found in association with pernicious anaemia of pregnancy. Such patients are frequently admitted as emergency cases and may not have been seen previously at a clinic. It is understandable, in these circumstances, that the clinician may overlook the primary nature of the anaemia.

The clinical history may give little help in the diagnosis although a story of increasing anaemia, particularly when associated with gastro-intestinal disturbance, should arouse suspicion. During the course of the present investigation many women were examined in whom the history was highly suggestive of pernicious anaemia of pregnancy, but the diagnosis was later disproved.

There are no clinical features which point unequivocally to the diagnosis. The yellow colour seen in true pernicious anaemia has, in my experience, been the exception rather than the rule. Enlargement of the spleen may be suggestive, but may also occur in puerperal anaemia due to sepsis. The diagnosis must depend therefore on a full haematological investigation. The majority of cases described in the past have been diagnosed by the presence of a true pernicious anaemia blood picture, but recent reports have shown that some of the typical features may be lacking. The value of the examination of the peripheral blood is therefore limited. The orthochromic normocytic picture which may occur may be simulated by a post-haemorrhagic anaemia

or anaemia due to sepsis or pregnancy toxaemia. The occasional low colour index may suggest a primary iron deficiency.

Even more detailed investigations involving estimation of the mean cell volume and mean cell diameter may not help greatly. A low M.C.V. is certainly against the diagnosis of pernicious anaemia of pregnancy, but a normal value does not exclude it, and a high value is not completely diagnostic of the condition. For instance, two patients with puerperal anaemia secondary to sepsis had an M.C.V. of 108·7 μ^3 and 113·4 μ^3 respectively, that is, higher than eight of the 12 values estimated in my patients with pernicious anaemia of pregnancy. The Price-Jones curves drawn for my series show how seldom a typical curve with a shift to the right and widening of the base is encountered, and a curve which would pass for normal is compatible with the diagnosis. Even a definite megalocytic hyperchromic blood picture is not completely diagnostic, for a further patient was encountered in whom anaemia gradually developed after a miscarriage and steadily progressed in spite of treatment. She had a high colour index anaemia with an M.C.D. of 7·9 μ, leucopenia, and thrombocytopenia. Sternal puncture, the subsequent course of the illness, and finally necropsy showed that she had panmyelophthisis and not pernicious anaemia of pregnancy as was originally thought.

One feature alone in examination of the peripheral blood can be relied on to establish the diagnosis. This is the presence of true megaloblasts in the blood-film. In several of the atypical cases in the present series the diagnosis would have been doubted had these cells not been found. For example, one woman was admitted with severe pre-eclamptic toxaemia and later developed a breast abscess. She had a low colour index anaemia (C.I. = 0·76), a polymorphonuclear leucocytosis, and little variation in size and shape of the red cells. The blood-films, however, showed the presence of numerous typical megaloblasts (Plate 6, Fig. 10). The presence of such cells was relied on for the ultimate diagnosis of 13 patients in my series. But even after a careful and prolonged examination of the blood-film megaloblasts may not be found, and it is in these circumstances that examination of the bone-marrow assumes particular importance. As the final diagnosis may depend entirely on the results of sternal puncture, it is important to decide how far the marrow changes may be regarded as significant.

The patient who is most likely to be referred for a detailed haematological examination is one who is becoming progressively more anaemic in spite of iron therapy and perhaps also transfusion. Various other complications may temporarily have claimed the attention of the obstetrician, with the result that the anaemia is fully developed by the time that the first blood examination is made. In such cases the appearance of the bone-marrow is unmistakable. Both the megaloblastic change in the red-cell precursors and the characteristic white-cell changes are seen at a glance. The extent of the changes appears to have no relation to the peripheral blood picture, and indeed two of my patients who showed the most marked megaloblastic reaction had the least typical blood findings. Markoff (1939) and Alder (1939)

have doubted the occurrence of a megaloblastic change in cases like these, which lack the features of true pernicious anaemia. They refer to such cases as 'pseudoperniziöse Gravitätsanämie', and describe the reaction in the bone-marrow as macronormoblastic. This is certainly not confirmed by the findings in my cases. Nearly all those in which a sternal puncture was made could be classified as 'pseudoperniziöse Gravitätsanämie', and yet they showed a definite megaloblastic reaction. It is conceivable that in certain circumstances this change may not be so clearly defined. If more frequent routine blood-counts were made during pregnancy and the puerperium the anaemia might be diagnosed at its onset when the megaloblastic reaction was first appearing. It also seems likely that cases occur in which there is only a partial lack of production or utilization of the anti-pernicious anaemia factor, and in these the megaloblastic change would be less marked.

Other patients may be seen at the commencement of a spontaneous remission, evidence of which may be present in the peripheral blood. In one of my patients the marrow contained very few typical megaloblasts, which were found only after careful examination of the film. At the same time there was an active erythroblastic reaction, the picture resembling that of the marrow from patients responding to treatment. The number of megaloblasts in the marrow from this patient was small, only 2·5 per cent. In some of Segerdahl's (1941) cases it was even smaller, and she has made the diagnosis of pernicious anaemia of pregnancy when typical megaloblasts have been as few as 1·0 and 0·6 per cent.

The question arises as to whether this number can be considered pathognomonic of pernicious anaemia of pregnancy, for Daniachij (1936*a*) has reported an apparent megaloblastic reaction in the marrow of normal pregnant women. This he found reached a maximum in the seventh to eighth month, and the percentage in his 32 patients varied from 0·1 to 1 per cent. Russo (1937) also classified some cells as megaloblasts in normal pregnancy marrows, but he admitted that these were all large cells in mitosis whose nature could not easily be determined. These findings have not been confirmed by the few others who have studied the marrow in normal pregnancy (Hansen, 1938; Forssell, 1939; Pitts and Packham, 1939; Markoff, 1939), but in order to decide this point personally I have done a sternal puncture on 19 healthy women at various stages of pregnancy and the puerperium. The results will be reported in detail elsewhere. I have found no evidence of a megaloblastic reaction at any time during normal pregnancy, although some of the marrows contained macronormoblasts showing premature haemoglobinization, and in others pro-erythroblasts were relatively easily found. Daniachij's (1936*a*) photograph of a 'megaloblast' from one of his patients suggests that the cells which he has grouped under this heading could be regarded as large basophil erythroblasts or pro-erythroblasts rather than true megaloblasts. It therefore seems safe to regard the appearance of even small numbers of typical megaloblasts in the marrow as a true pathological change during pregnancy.

Having established this fact, it is also necessary to consider whether the changes in the marrow are quite distinct from those found in other anaemias of pregnancy. The frequent association of pernicious anaemia of pregnancy with complications such as sepsis and toxaemia, which in themselves may give rise to anaemia, makes it particularly important to be able to differentiate the pernicious anaemia cases. I have found that the megaloblastic appearance of the marrow is quite specific, and that in other cases in which the history and peripheral blood findings have suggested pernicious anaemia of pregnancy, a report to the contrary on the basis of marrow examination has been confirmed by the response to treatment other than liver. For instance, a patient with mastitis was severely anaemic and from her blood-count might have been diagnosed as a case of pernicious anaemia of pregnancy. Her marrow, however, showed a pronounced leucoblastic reaction with very frequent mitotic figures. The granular cells showed some anisocytosis, but the giant forms were not the atypical leucocytes of pernicious anaemia and the erythroblasts were all normal in type. Rapid recovery followed a blood-transfusion and incision of the abscess. *Staphylococcus aureus* was cultured from the pus. In another suspected case the patient had had an ante-partum haemorrhage, but it did not appear that her blood loss could account for her very severe anaemia. She also had a history of severe anaemia in her last pregnancy. Her marrow, however, showed a pure normoblastic reaction. She improved on iron therapy alone. Some women with severe anaemia and pregnancy toxaemia were also examined. Again the reaction in the marrow was normoblastic, the characteristic cell being rather small with a dense pyknotic nucleus. In these and similar cases, without the help of sternal puncture, the diagnosis of pernicious anaemia of pregnancy would probably have been made, and they might have been cited as examples of spontaneous recovery. The diagnostic significance of the changes in the bone-marrow cannot, therefore, be over-emphasized.

Prognosis

Before the days of safe blood-transfusion and liver therapy the immediate prognosis in pernicious anaemia of pregnancy was poor, but since specific therapy has been introduced very few fatalities have been recorded. Two of Stevenson's series of 30 patients died, but neither of them was given a transfusion (Stevenson, 1938). One death in the series of Davidson, Davis, and Innes (1942*b*) was attributed to septic complications, the other followed a transfusion reaction. Three of my patients died, but in two of them the diagnosis was made only at necropsy. One had been in hospital for four weeks with the clinical diagnosis of aplastic anaemia, the other was admitted to hospital *in extremis*. Neither had received any specific therapy. In the third fatal case the anaemia was of rapid onset at the end of pregnancy. While the patient was being given a blood-transfusion labour pains began. Her condition rapidly deteriorated and she died undelivered.

The ultimate prognosis has always been recognized as good, and indeed this was one of the first distinguishing features to be pointed out between pernicious anaemia of pregnancy and Addisonian anaemia (Osler, 1919). The risk of recurrence in further pregnancies has been emphasized by some observers. This view appears to be well founded, for there are nearly twice as many records of recurrence as of further normal confinements. In the two instances of proven recurrence in the present series the women had conceived again almost as soon as they had recovered from the first illness.

Segerdahl (1941) has described a recurrence of the anaemia in one woman on two occasions apart from a further pregnancy. Similarly one patient in my series had a relapse of the anaemia unassociated with pregnancy on two occasions three years and three and a half years after apparent complete recovery. Each relapse coincided with the development of a urinary infection. When last seen she had received no treatment for a year and a half and had remained extremely well. In both these women free hydrochloric acid was present in the gastric secretion contra-indicating the diagnosis of Addisonian anaemia beginning in pregnancy. It is possible that the 'hypoplastic anaemia of pregnancy' described by Whitby (1932) was of a similar nature. There was unfortunately no evidence of the state of the bone-marrow in his patient, but she relapsed on more than one occasion after her initial recovery and responded each time to treatment with liver. Each relapse coincided with an intercurrent infection.

Strauss (1935) had two patients who recovered completely from pernicious anaemia of pregnancy, but after a period of years developed true pernicious anaemia. One patient in my series still had megalocytosis and a shift to the right of her Price-Jones curve after recovery from her anaemia. This aroused suspicion that she was really suffering from Addisonian anaemia beginning in pregnancy. Unfortunately she was a particularly uncooperative patient, refusing a fractional test meal and ceasing to attend for blood-counts three months after stopping treatment. It seems likely, however, that she may relapse and prove to have true pernicious anaemia.

With regard to the prognosis for the child, most reports indicate that premature delivery and stillbirths are particularly frequent. In Stevenson's series of 30 patients there was one miscarriage and eight premature births. Five babies were stillborn and there was one additional neonatal death (Stevenson, 1938). In my series labour was premature in only six cases, four being the result of surgical induction for toxaemia of pregnancy. One baby died *in utero* as a result of the mother's death, but all the other babies were born alive. There was only one neonatal death.

Treatment

Bardy (1924) reviewed the earlier methods of treatment. These included iron and arsenic by mouth and by injection, bone-marrow, subcutaneous and intramuscular injections of blood and serum, autohaemotherapy and transfusions. While none of these remedies was of any lasting benefit during

pregnancy, a remarkable spontaneous remission sometimes occurred after delivery, even in patients who had appeared practically moribund with a haemoglobin value of less than 20 per cent. The administration of large blood-transfusions greatly improved the prognosis (Larrabee, 1925). Whitby (1932) suggested that they had a specific curative action, but there seems to be little evidence to support this view. Before delivery transfusions alone have never produced more than a temporary improvement in the blood condition, and after delivery even repeated blood-transfusions have not always been followed by a remission (Filo, 1931). Nevertheless, transfusions have been of great value in acutely ill and gravely anaemic patients, and in those who have been slow to respond to more specific therapy.

Although many patients have shown a response to liver treatment comparable with that found in true pernicious anaemia, the results in some cases have been less satisfactory. Improvement has sometimes been observed before delivery (Brault, 1928; Devraigne and Laennec, 1928; Beckman, 1928; Peterson, Field, and Morgan, 1930; Dyke, 1931; Stevenson, 1938; Segerdahl, 1941), but where the liver treatment has been discontinued before term a relapse has occurred. Abramson (1938) gave one of his patients large doses of liver extract during the last month of pregnancy, but was unable to raise the haemoglobin above 60 per cent.; a complete remission followed delivery. Others have treated patients with liver before delivery with little or no improvement (Meaker and Bongiorno, 1929; Kersley and Mitchell, 1934; Barnum and Woodward, 1938; Föderl, 1938; Ritter and Crocker, 1939; Nos. 15 and 21 of the present series). Ritter and Crocker's patient was admitted with anaemia at the sixth month of pregnancy. She received three transfusions and, in all, 76 c.c. of liver extract before delivery, but showed no definite response until the puerperium. The anaemia may prove refractory to treatment for periods varying from weeks to months (Ungley, 1938; Dockeray, 1938; Nielsen, 1941; Davidson, Davis, and Innes, 1942*b*; Fullerton, 1943). Two points have received particular attention with regard to this refractory behaviour. In the first place, it has been suggested that sepsis may be the inhibitory factor, and secondly the type of preparation and the route of administration of the liver have been considered important.

Haemoglobin production in anaemic dogs may be completely inhibited by the presence of an infection such as endometritis and temporarily inhibited by a sterile abscess (Robscheit-Robbins and Whipple, 1936; Whipple, 1938). In Addisonian anaemia sepsis, in particular infection of the genito-urinary tract, has been found to retard the response to liver therapy (Beebe and Lewis, 1931; Minot and Castle, 1935; Wintrobe, 1942). Pyelitis is a relatively common complication of pregnancy, and in the puerperium many forms of infection are likely to occur. It is a natural conclusion, therefore, that sepsis may be the inhibitory factor in refractory cases of pernicious anaemia of pregnancy. Of those who have commented particularly on such cases, Davidson, Davis, and Innes (1942*b*) do not regard infection as of prime importance, though they admit that nine of their 16 patients had

some septic complication and that in one particularly refractory and eventually fatal case, death was attributable to severe bronchiectasis and pyelonephritis. On the other hand, Fullerton (1943) found no sepsis in his three refractory cases, and one of Nielsen's patients, though slow to respond at first, improved later and maintained a good blood level in spite of the fact that she developed a tuberculous pleurisy (Nielsen, 1941). Sepsis was not present in Ritter and Crocker's (1939) patient, who showed no response until after delivery.

Eight of my patients showed no response to treatment for at least 14 days, the longest refractory period being six weeks. Of the two who showed the greatest delay in response, one is particularly interesting. She had a *Streptococcus viridans* infection of her neck, and received massive doses of liver extract for three weeks before delivery, with no response. On an analogy with Ritter and Crocker's case one might have expected a rapid improvement after delivery. It was not, however, until two weeks later that she eventually began to improve, and then only after the abscess, which had previously been insufficiently drained, was re-incised and the pus properly evacuated. The evidence in this case, therefore, seems strongly in favour of sepsis having exerted an inhibitory influence. The effect of sepsis was also noted in a further patient, who improved after incision of a breast abscess whereas before, in spite of two blood-transfusions, the haemoglobin had fallen to the original level within 10 days. One woman had a history which was more difficult to interpret. She had a heavy urinary infection which for some weeks was held to be entirely responsible for the anaemia. The urine was eventually sterilized with sulphathiazole, and the blood-count which had previously been falling at an alarming rate remained fairly steady for two weeks with no other medication. When sulphathiazole treatment was stopped, pus reappeared in the urine and the haemoglobin began to fall once more. Later, liver was given parenterally, but was ineffective until the urine was finally sterilized and kept sterile by continuous small doses of sulphathiazole. At the same time, however, the improvement accompanied the addition of Liveroid by mouth, and it might be interpreted that the oral therapy supplied some haemopoietic factor which was missing in the parenteral liver extract. A septic focus could actually be demonstrated, with one exception, in all those in my series who showed a delayed response; this woman improved rapidly after delivery. The others had a variety of infections such as mastitis, pyelitis, endometritis, and cervicitis. In most of these patients there was not a sufficiently clear correlation between improvement in the blood condition and removal of the sepsis to be able to conclude that the infection was the chief inhibitory factor. It is certain that in at least two patients a purulent vaginal discharge persisted after recovery from the anaemia. Sepsis was also present in some cases in which the response to treatment was rapid. In most of these, measures were adopted to deal with the infection at the same time as treatment was started, but one patient developed a puerperal thrombophlebitis which did not affect the speed of

recovery. Such evidence suggests that it is particularly important to look for and deal with all possible sepsis in pernicious anaemia of pregnancy. After elimination of this factor, however, there still remain cases in which recovery is slow, and for these some further explanation must be sought.

It has been suggested that pure extracts of liver may be less effective in treatment than crude extracts and, more particularly, that oral liver therapy is effective where parenteral therapy has failed (Ungley, 1938; Miller and Studdert, 1942; Fullerton, 1943). There was no convincing evidence in my series that either of these factors was important, although improvement in one patient did coincide with the addition of oral therapy. But this result was inconclusive for, as has already been discussed, a urinary infection was also present and had almost certainly inhibited the response to treatment. In two patients there was a suggestion that the change from the pure extract Anahaemin to the crude extract Campolon initiated the response, but blood-counts were unfortunately not made at sufficiently frequent intervals to establish this point. On the occasion of her second relapse, one patient showed a rapid fall of haemoglobin in spite of treatment with Anahaemin. This was particularly surprising in that she had on a previous occasion apparently responded to Anahaemin. This time improvement did not occur until the preparation was changed to Campolon, but here again there was the complicating factor of a urinary infection, and a claim that Campolon supplied some necessary factor which was missing in Anahaemin must be made with reservation. Controlled therapeutic experiments are particularly difficult in this disease. The women are often desperately ill and one is tempted to give massive oral and parenteral therapy in refractory cases. The presence of complications makes the interpretation of the results even more difficult. Furthermore, some patients in whom the preparation of liver has not been varied have eventually shown a satisfactory response, indicating that prolonged control periods are necessary before any particular preparation may be considered as ineffective.

Apart from liver treatment, marmite and hog's stomach preparations have both been found to give good therapeutic results in some cases (Wilkinson, 1932; Rowland, 1933; Strauss and Castle, 1933; Stevenson, 1938; Ungley, 1938; Doan, 1938; Miller and Studdert, 1942). While this is of theoretical interest, from a practical point of view liver treatment will usually be the method of choice. Patients who are severely anaemic, and may in addition have some gastro-intestinal disturbance, are likely to find these oral preparations unpalatable and difficult to take in the required quantities. Liver treatment should be continued at least until a good reticulocyte response has been obtained. In many cases this is probably all that is necessary, but one of Fullerton's (1943) patients had a reticulocyte response of 27·5 per cent. which was not followed by a remission. After further treatment a second response was obtained and improvement followed. It therefore seems preferable to continue treatment until the blood-count has returned to normal.

Discussion

The relationship between pernicious anaemia of pregnancy and tropical and subtropical macrocytic anaemia. The macrocytic anaemia of pregnancy occurring in tropical and subtropical countries has generally been considered as a disease distinct from pernicious anaemia of pregnancy occurring in temperate climates. One of the main reasons for the distinction has been the fact that the tropical anaemia is found also in men and non-pregnant women. Several studies have been made of the macrocytic anaemia occurring in India (Balfour, 1927; McSwiney, 1927; Wills and Mehta, 1929; Wills and Talpade, 1930; Wills, 1931, 1932, 1933; Gupta, 1932; Mitra, 1937; Wills and Evans, 1938; Napier, Gupta, Chaudhuri, Sen, Chaudhuri, Gupta, and Majumder, 1938; Napier, 1939; Hare, 1939; Mudeliar and Menon, 1942), in Macedonia (Fairley, Bromfield, Foy, and Kondi, 1938; Foy and Kondi, 1939), and on the Gold Coast (Russell, 1941), particularly in relation to pregnancy. Many of the cases described have been complicated by malaria, hookworm, or other parasitic infection, with resulting modification in the blood picture. Thus the Macedonian patients described by Fairley, Bromfield, Foy, and Kondi (1938) showed a haemolytic blood picture with a high reticulocyte count and raised bilirubin in the plasma. The very high incidence of associated malaria appeared to account for these features. Several of the Indian cases of Mudeliar and Menon (1942) were complicated by iron deficiency, for example, due to ankylostomiasis, and in these a macrocytic hypochromic anaemia was characteristic. Wills (1931) was careful to exclude patients with such complications in her description of the syndrome. She pointed out various features which distinguished her cases from Addisonian anaemia. The age incidence was earlier, the blood was macrocytic but showed, as a rule, less anisocytosis and poikilocytosis than the average case of true pernicious anaemia. There was no increase in the plasma-bilirubin, the tongue frequently appeared normal, free hydrochloric acid was usually present in the gastric secretion, there were never any signs of involvement of the nervous system, and the pregnant patients showed a tendency to spontaneous remission after delivery. In general these features apply equally well to my own series of cases of pernicious anaemia of pregnancy. In addition, in both Wills's and my patients the initial reticulocyte counts were low.

The Price-Jones curves from the majority of the Macedonian cases showed a normal or only slightly increased mean cell diameter. Most of the sternal puncture and post-mortem findings are reported only briefly, but Fairley, Bromfield, Foy, and Kondi (1938) have described the marrow in some detail in their patients. They found both a megaloblastic reaction and the characteristic white-cell changes of pernicious anaemia.

The Indian and Macedonian cases have generally been accepted as nutritional in origin. This view has been based on Wills's work. She correlated the incidence of the anaemia with the nutrition of the patients and showed

that administration of marmite produced a dramatic improvement in the blood picture (Wills, 1931, 1933). Later she was able to produce experimentally a macrocytic anaemia in Rhesus monkeys by giving them a diet based on that taken by the poor Mohammedans in Bombay (Wills and Bilimoria, 1932; Wills and Stewart, 1935). This anaemia was also cured by marmite. Further experiments showed that the anaemic monkeys and patients with tropical macrocytic anaemia would not respond to Anahaemin, but would improve on a crude liver extract such as Campolon (Wills, Clutterbuck, and Evans, 1937; Wills and Evans, 1938). Wills concluded, therefore, that the anaemia was entirely nutritional in origin, being due to a deficiency in a factor contained in autolysed yeast (marmite) and Campolon, but not in Anahaemin. Though these therapeutic experiments seem conclusive, they have not been entirely confirmed by other workers. The Macedonian cases did respond to marmite, but only when given in very massive doses. On the other hand they improved on both crude liver extracts and Anahaemin (Foy and Kondi, 1939). Some of the Indian cases reported by Mudiliar and Menon (1942) showed practically no response to marmite, but improved rapidly on liver extract, whether crude or purified. At the same time these authors noted that 22 of their patients had an adequate diet with no lack of protein or vitamin B complex. Similar contradictory results have been obtained in the treatment of patients with pernicious anaemia of pregnancy in temperate climates. None of my patients was treated with marmite, but cases have been reported in which the response to such treatment has been exactly comparable with that obtained by Wills (Ungley, 1938; Doan, 1938; Miller and Studdert, 19[illegible]). Others have been treated with autolysed yeast extract first with n[illegible], but have later improved on the addition of normal gastric juic[illegible] extract (Strauss and Castle, 1933; Miller and Studdert, 1942). P[illegible] extracts alone have been found effective in some women, but [illegible]ggestion that crude extracts may sometimes b[illegible] T[illegible]tive [illegible] [illegible]acts, or that oral liver therapy may even be [illegible] [illegible]il or [illegible]2; Fullerton, 1943). Whereas most patien[illegible] [illegible]ly im[illegible] [illegible]eatment before delivery, Fairley, Bromfic[illegible] Kond[illegible] that in the Macedonian cases such im[illegible] slow [illegible] large doses of liver, until after confine[illegible] [illegible]ases [illegible]es an incomplete response has been [illegible]n [illegible]ry and occasional uncomplicated ca[illegible] even to massive therapy, before [illegible] Föderl, 1938; No. 15 of the presen[illegible] the tropical anaemia and the pernic[illegible] of liver required seems to be greatly in[illegible] case of Addisonian anaemia. There se[illegible] parallel between these two groups of ma[illegible] variation in blood picture and response to t[illegible] lationship between them will be further disc[illegible]

Aetiology

Various theories have been advanced to explain the pathogenesis of pernicious anaemia of pregnancy. In the past it has been regarded as a primary haemolytic anaemia (Minot, 1921; Rowland, 1924; Allan, 1928; Witts, 1932; Swan, 1933), but although, as in true pernicious anaemia, the possibility of a haemolytic component cannot be overlooked, the megaloblastic change in the bone-marrow leaves little doubt that this is primarily a dyshaemopoietic anaemia due to lack of the anti-pernicious anaemia factor. Since, according to Castle's hypothesis, this may result from dietary deficiency, intrinsic factor deficiency, or interference with absorption or utilization of the factor, there are several possibilities which have to be considered in relation to the aetiology.

Nutritional deficiency. It is natural that some attempt should be made to correlate the rare pernicious anaemia of pregnancy of temperate climates with the commoner form of the tropics; accordingly emphasis tends to be laid on the aetiological importance of nutritional deficiency. The occurrence of a similar macrocytic anaemia in men and non-pregnant women in India, Macedonia, and occasionally also in temperate zones (Groen and Snapper, 1937) certainly adds weight to the argument that dietary deficiency is of prime importance. There are, however, various anomalies which make it difficult to accept this view of the aetiology in every case.

It is true that the incidence of pernicious anaemia of pregnancy is particularly high in those parts of the world where the diet is especially poor. In this country nearly all the reported cases have been from poor hospital practices, and the majority of my cases formed no exception to this. Gastro-intestinal disturbances, producing relative dietary deficiencies, are also notably frequent. On the other hand, for every patient who develops pernicious anaemia of pregnancy there are numerous others who remain well on a similar or even worse diet. In addition, in a few cases, even in India, the diet has apparently been satisfactory. In one of my patients, for instance, any nutritional deficiency seemed to be positively excluded. Her appetite had been good, she had had no gastro-intestinal disturbance, her protein and vitamin intake had been adequate, and she had had additional iron and vitamin C throughout pregnancy. Her plasma-proteins were estimated at monthly intervals and the values remained well within normal limits. If the anaemia were due primarily to a dietary deficiency, one might expect more frequent associated signs of malnutrition. Though four of my patients were thin, only one showed additional signs which might have been due to a defective diet. She had diarrhoea, a dry skin, oedema, and a low plasma-protein. Her condition was so critical that no trial was made with dietary treatment alone.

The failure of some observers to confirm the favourable results obtained by Wills (1931, 1933) and Ungley (1938) with marmite treatment also suggests that many cases are not simply nutritional in origin. The problem is further

complicated by the fact that Wintrobe (1939) has shown that yeast extract may have a haemopoietic effect even in cases of true pernicious anaemia. It seems apparent that, while in some instances gross dietary deficiency may be of prime importance in the aetiology, in the majority of cases it constitutes at most only a predisposing factor.

Intrinsic factor deficiency. The question of intrinsic factor deficiency has been investigated by Strauss and Castle (1933) in eight patients with macrocytic anaemia of pregnancy. They concluded, as the result of therapeutic experiments, that there was a temporary lack of secretion of intrinsic factor during pregnancy with a partial return after delivery and complete recovery later. They did not demonstrate the lack of intrinsic factor directly, but inferred this from the response to treatment with beefsteak plus normal gastric juice in one patient, and autolysed yeast plus normal gastric juice in another, after failure to respond to beefsteak plus hydrochloric acid and autolysed yeast plus hydrochloric acid. In earlier work they had demonstrated the frequency with which the normal gastric secretion is depressed during pregnancy, and it seemed likely that a similar disturbance of secretion of intrinsic factor might occur (Strauss and Castle, 1932 *a*, *b*).

It would not be necessary to postulate complete absence of intrinsic factor during pregnancy in every patient who developed the pernicious type of anaemia. With an adequate diet and an uncomplicated pregnancy a woman with hyposecretion of intrinsic factor might be able to produce just enough anti-pernicious anaemia factor to prevent the occurrence of anaemia. The margin of safety would, however, be narrow, and since the foetus is dependent on the mother for haemopoietic principle, the balance would become more precarious as the pregnancy progressed. Any factor such as haemorrhage, sepsis, toxaemia, or multiple pregnancy, which puts an added strain on the haemopoietic system and increases the demands for anti-pernicious anaemia factor, would then precipitate the onset of pernicious anaemia of pregnancy. Alternatively if, in addition to hyposecretion of intrinsic factor, the diet were defective or vomiting had been frequent, the chances of sufficient anti-pernicious anaemia factor being produced would be greatly diminished.

In my series of patients there have been some striking instances of a sudden breakdown under an added strain. For example, one patient maintained a fairly steady blood level until she developed pre-eclamptic toxaemia in the last few weeks of pregnancy. Another woman also became anaemic with the onset of toxaemia; in addition, she had twins and must therefore have had to supply a greater quantity of anti-pernicious anaemia factor. A third had been well up to the time of delivery, but became rapidly anaemic when she developed a severe urinary infection. Another remained well in her third pregnancy until she developed an abscess in her neck. This theory of a temporary intrinsic factor deficiency during pregnancy does not, however, fit in with all the facts related to the anaemia. Such a deficiency should be adequately remedied by treatment with potent liver extracts, but

while many cases of pernicious anaemia of pregnancy do respond quickly to liver treatment, others are refractory for varying lengths of time.

Endocrine influences. It is generally accepted that pregnancy is accompanied by considerable endocrine disturbance and by noteworthy changes in the pituitary gland. It is not clear what connexion the pituitary may have with the haemopoietic system, but both experimental and clinical observations have suggested that a relationship does exist between the two. Meyer, Stewart, Thewlis, and Rusch (1937) found that hypophysectomized rats developed anaemia and a subnormal reticulocyte count. These animals failed to show the normal hyperplasia of the haemopoietic tissue after exposure to low oxygen tension. Flaks, Himmel, and Zlotnik (1937) obtained a reticulocyte response and increase in red cells in rats by oral administration of anterior pituitary, while a similar response was not seen in a control series fed with liver.

More significant than these, however, are the observations of Dodds, Noble, and Smith (1934), Dodds and Noble (1935), Dodds, Hills, Noble, and Williams (1935), and Dodds, Noble, Scarff, and Williams (1937). They found that rabbits injected with pituitrin developed lesions in the acid secreting area of the stomach and that some of the animals developed in addition a severe macrocytic anaemia. This work has been criticized by Gilman and Goodman (1937), who suggested that the blood changes could be explained on the basis of water retention. Further work by Dodds, Liu, and Noble (1938) has shown that this explanation is unlikely. In addition to these experiments, which suggest that the pituitary may have some influence on blood formation, the effect of ovarian hormones on the haemopoietic system has also received attention. Anaemia and thrombocytopenia have been produced in dogs by administration of large doses of follicular hormone (Arnold, Hamperl, Holtz, Junkmann, and Marx, 1937; Schrade, 1938). It is difficult to relate these changes to any naturally occurring conditions as the doses of hormone used were so large. Steinglass, Gordon, and Charipper (1941) have, however, shown that in rats the blood picture is related to the sex of the animal, and their bone-marrow studies suggest that androgens stimulate and oestrogens inhibit erythropoiesis.

On the clinical side pernicious anaemia has been found in association with various endocrine disturbances, notably myxoedema (Means, Lerman, and Castle, 1931; Bomford, 1938), thyrotoxicosis (Meulengracht, 1929; Meulengracht and Hartfall, 1934), and pituitary insufficiency (Snapper, Groen, Hunter, and Witts, 1937; Witts, 1942). It has been suggested that gastric changes associated with the anacidity which is a common finding in all these conditions, lead to the anaemia rather than that the anaemia is the direct result of the endocrine disturbance. During pregnancy it may well be that the frequent disturbance of gastric secretion (Strauss and Castle, 1932*a*, *b*; Strauss, 1934; Davies and Shelley, 1934) is related to a pituitary influence which may, in some cases, also reduce the secretion of intrinsic factor. This offers an explanation for the spontaneous recovery which tends to occur

after delivery when the endocrine balance returns to normal, but again the occasional failure to respond to adequate substitution therapy remains a problem.

It has already been suggested that sepsis exerts an inhibitory influence in certain of the refractory cases, but there are a few in which no such explanation can be given, notably those in which response is delayed until after delivery. Wintrobe and Schumacker (1935) have explained the anaemia on the basis of the fact that the mother has to meet the requirements of the foetus for anti-pernicious anaemia factor in addition to her own. While this would account for the spontaneous remission which tends to occur after delivery, it cannot explain the failure of substitution therapy. It appears that in these refractory cases, as in the cases described by Israëls and Wilkinson (1936, 1940) as achrestic anaemia, there is an inability of the patient to utilize the haemopoietic substance. An inhibitory influence, intimately connected with pregnancy, may be postulated, and it seems reasonable to suppose that such an influence is endocrine in origin. The experimental evidence that oestrin interferes with haemopoiesis suggests the possibility that this may be the hormone involved. If the presence of such an inhibitory influence is accepted, one may further postulate all degrees of interference in utilization of the anti-pernicious anaemia factor. Under a strong influence the patient would remain completely refractory until the hormone levels became readjusted after the termination of pregnancy. A weaker influence might, on the other hand, be overcome if sufficiently large quantities of anti-pernicious anaemia factor were administered. The fact that patients treated during pregnancy frequently require much larger quantities of liver than patients with Addisonian anaemia, and that they tend to relapse quickly unless treatment is continued until delivery, lends support to this idea. Again, any additional burden on the haemopoietic system, such as sepsis or haemorrhage, would tend to make the effect more marked and would precipitate a breakdown.

This theory of an inhibitory endocrine influence still leaves some points unexplained. In the first place, it is difficult to see why patients who have only a mild anaemia should not recover after delivery when the conditions which have given rise to the anaemia have been readjusted. Instead, the patient's blood-count may gradually deteriorate until she is given liver some months *post partum*. Even more puzzling are the few patients who have had a relapse of the anaemia apart from a further pregnancy. I am doubtful whether Whitby's (1932) suggestion that these are 'hypoplastic anaemias' is correct. Such an explanation awaits confirmation from sternal puncture, for the cases which he described as belonging to this type correspond closely with some of mine who were shown to have very cellular marrows. In one of Whitby's patients and in one of mine the relapses coincided with the onset of an infection. In Segerdahl's (1941) patient no such precipitating factor appeared to be present.

Haemolysis. While pernicious anaemia of pregnancy can no longer be

grouped among the primary haemolytic anaemias, the question of a haemolytic component in the pathogenesis of the anaemia should not be overlooked. Admittedly in my cases there has been no increase in the serum-bilirubin or plasma-bilirubin, no reticulocytosis before treatment, and the fragility of the red cells where tested has been normal. On the other hand, some patients have shown a rate of fall of haemoglobin (as much as 3 per cent. per diem in some cases) which could be accounted for only by an increased rate of blood destruction. In this connexion one of my patients, belonging to the blood group A, was given a transfusion of group O-cells with the object of following the survival of the red cells by the Ashby technique (Ashby, 1919). The average life of the transfused cells was found to be 25·9 days, while the average life of cells transfused to a control group of patients with hypochromic anaemia was about 50 days (Brown, Hayward, Powell, and Witts, 1944). The experiment was unfortunately carried out over a period when an active urinary infection was present. The increased rate of blood destruction may therefore have been partly due to the sepsis. It would be of interest to repeat this experiment in a further suitable patient in whom there was no such complicating factor.

Conclusions

A review of the clinical and haematological findings in pernicious anaemia of pregnancy has shown that the general conception of the illness must be revised. A blood picture identical with that of true pernicious anaemia is the exception rather than the rule, and in some cases the blood lacks all the characteristic features of this anaemia. On the other hand, the changes in the bone-marrow are closely comparable with those of Addisonian anaemia.

It is well to remember that pernicious anaemia of pregnancy may accompany a more obvious cause of anaemia such as haemorrhage, sepsis, or toxaemia of pregnancy. It is possible that such factors may precipitate the onset of the pernicious type of anaemia, and unless this is kept in mind the fundamental nature of a severe anaemia may escape recognition.

Any case of anaemia associated with pregnancy deserves a full haematological investigation. A similar blood picture may be encountered in a variety of conditions associated with pregnancy, and the only two features which may be relied on for the certain diagnosis of pernicious anaemia of pregnancy are the appearance of megaloblasts in the peripheral blood and the finding of a megaloblastic change in the bone-marrow. Marrow biopsy by means of sternal puncture is therefore of the greatest value in diagnosis, and without this procedure some cases will be overlooked while others will be treated unnecessarily with liver extract.

In treatment, the points to be emphasized are the necessity for giving adequate doses of liver extract and for continuing treatment until a satisfactory response has occurred, or preferably until the blood count is normal again. In refractory cases particularly careful attention should be paid to any foci of sepsis, especially urinary infection, and transfusions should be given to maintain a good blood level until the liver takes effect.

With regard to aetiology, it is difficult to advance any one theory which will meet every case. A haemolytic component probably plays a part, but the anaemia should at present be regarded primarily as a dyshaemopoietic anaemia. Malnutrition is important, but is probably only in the minority of cases the actual cause of the anaemia. It should be considered rather as a strong predisposing factor.

Strauss and Castle's theory of a temporary deficiency of intrinsic factor, though satisfactory in many respects, fails to explain the frequency with which cases are refractory to treatment with anti-pernicious anaemia factor. In many instances a focus of infection may be the inhibitory influence, but there are some patients in whom this is clearly not the case. Such patients behave temporarily like cases of achrestic anaemia. The cause of their failure to utilize the anti-pernicious anaemia factor is not understood. It does seem that the inhibitory influence is in some way connected with the pregnant state, and the suggestion is made that it is endocrine in origin, though the exact nature of the disturbance remains obscure.

The cases in my series have been reported in full in an M.D. thesis, which may be borrowed for reference from the University Library, St. Andrews.

I wish to thank Professor D. F. Cappell for his help and criticism and for putting at my disposal the records and preserved material from some of the earlier cases. I am also grateful to Professor L. J. Witts for his interest in the work and valuable advice in revision of the manuscript.

Members of the staff of various hospitals, notably those of Dundee Royal Infirmary and the Radcliffe Infirmary, Oxford, have kindly co-operated in allowing me access to case records and clinical material.

I am indebted to Joan F. Powell for the serum-iron estimations, and to others who have given me technical assistance.

I also have to acknowledge with gratitude a grant towards the costs of publication of this work received through the Directors of the Dundee Royal Infirmary from their Fund for Research on Diseases of the Blood.

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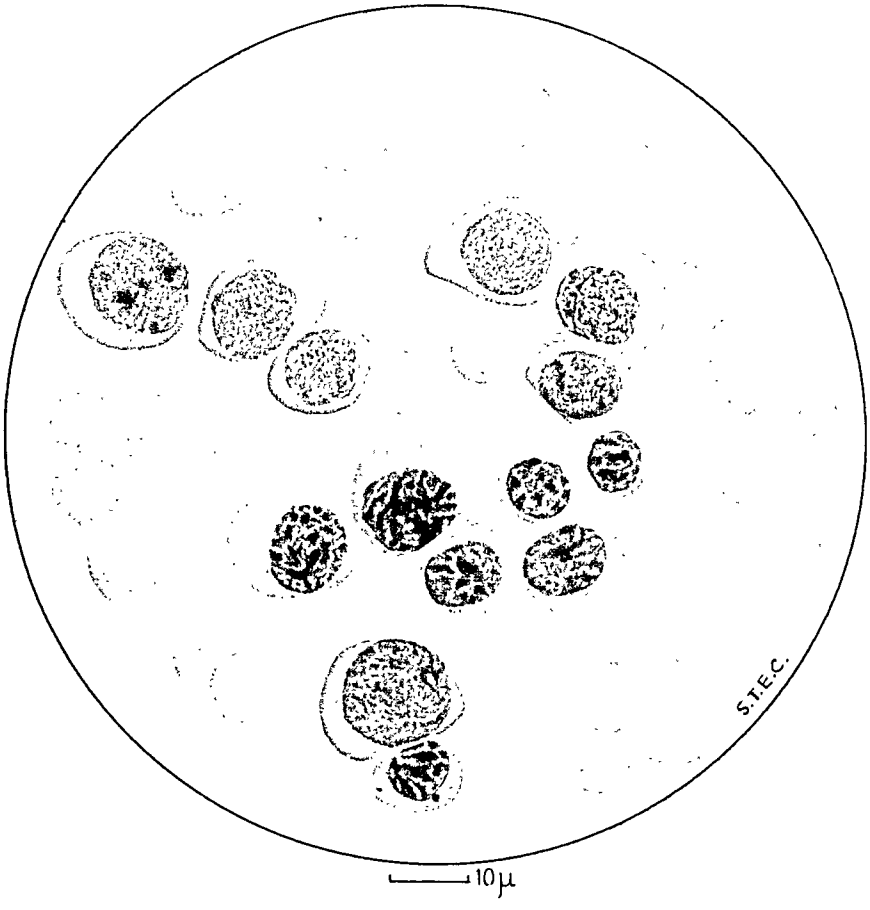


FIG. 9. Mixed megaloblastic and normoblastic erythropoiesis, five days after liver treatment had been started (Case 19). (Leishman stain)

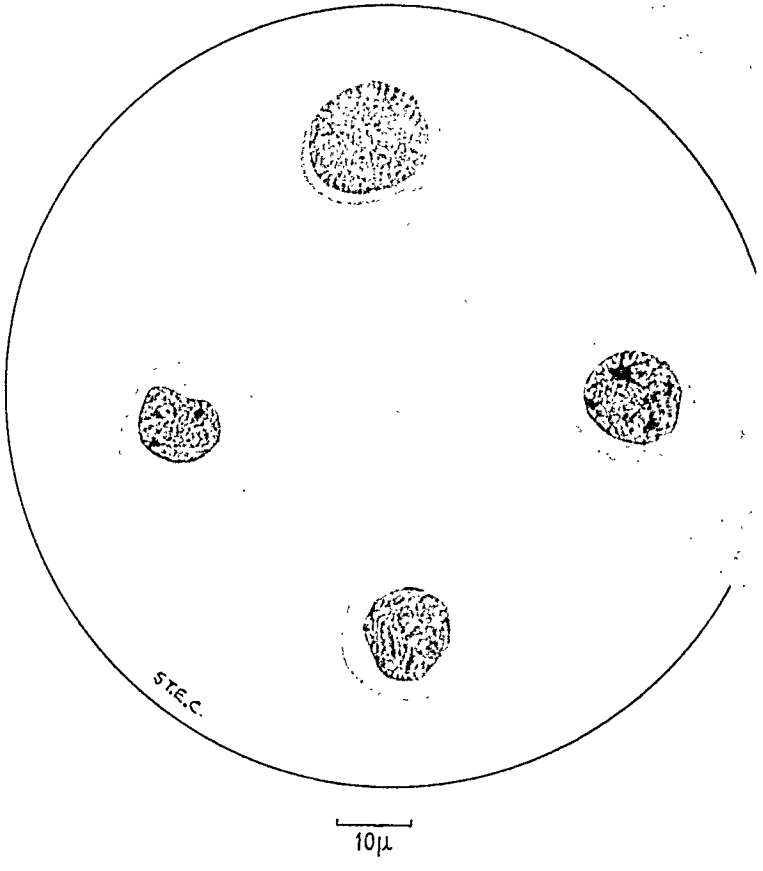


FIG. 10. Megaloblasts from the peripheral blood. Composite drawing from several fields (Case 12). (Leishman stain)

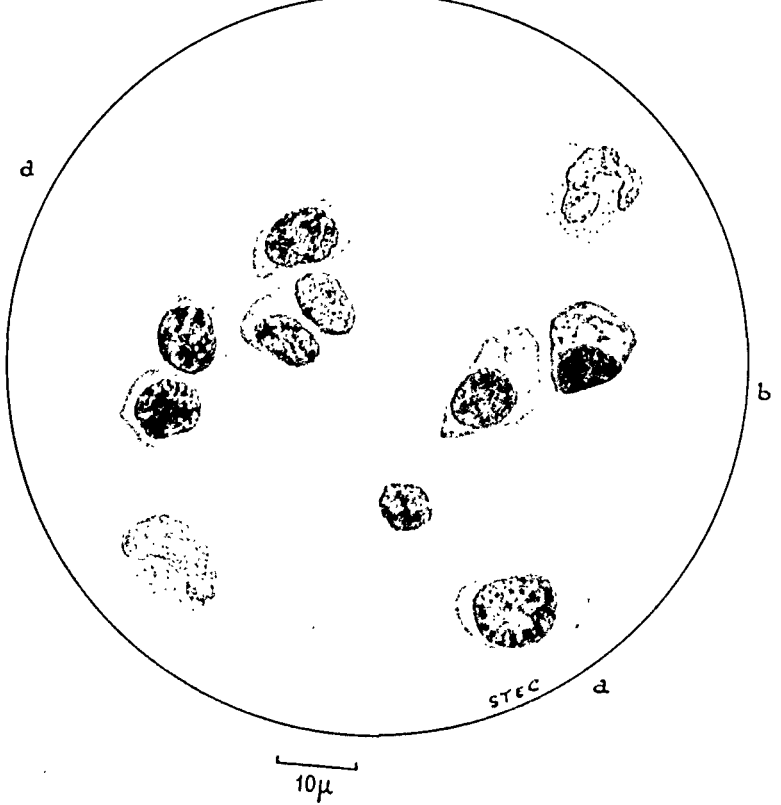


FIG. 7. Sternal marrow at five and a half months pregnancy, showing normoblastic erythropoiesis (Case 8). (*a*) Basophilic and polychromatophilic erythroblasts. (*b*) 'Plasmatoid' erythroblasts. (May-Grünwald, Giemsa stain)

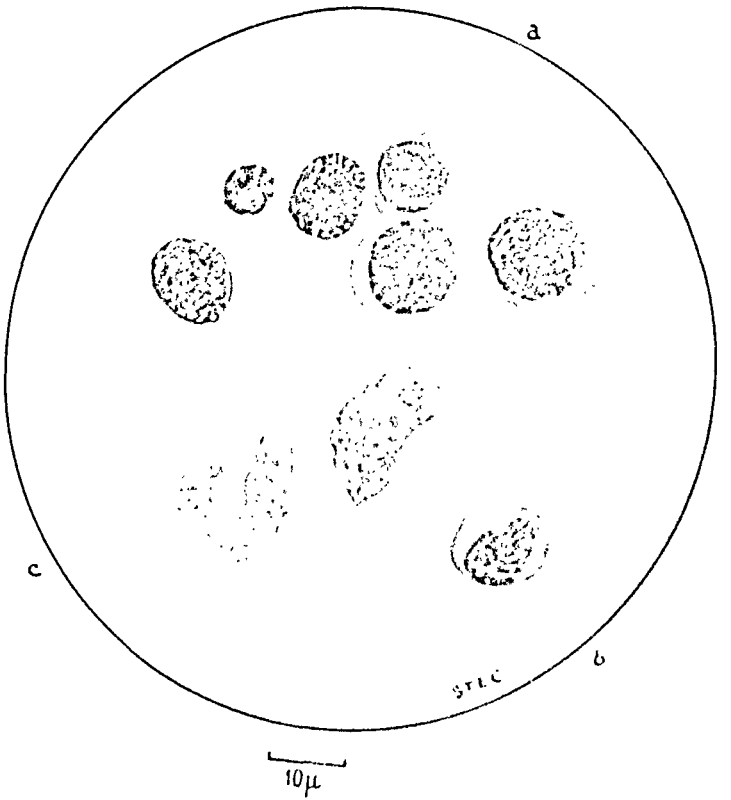


FIG. 8. Marrow from the same patient (Case 8) 10 days after delivery, showing (*a*) megaloblastic erythropoiesis, (*b*) degenerate form of megaloblast, (*c*) abnormal granulocytes. (May-Grünwald, Giemsa stain)

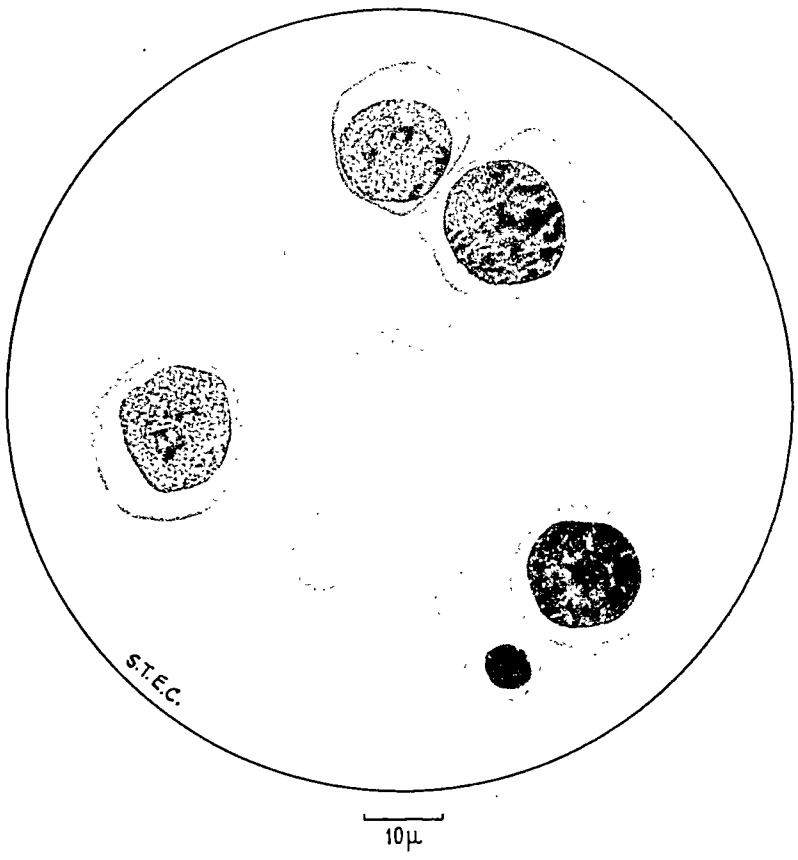


FIG. 5. Macronormoblastic type of erythropoiesis, early basophilic erythrocyte precursors. (Leishman stain)

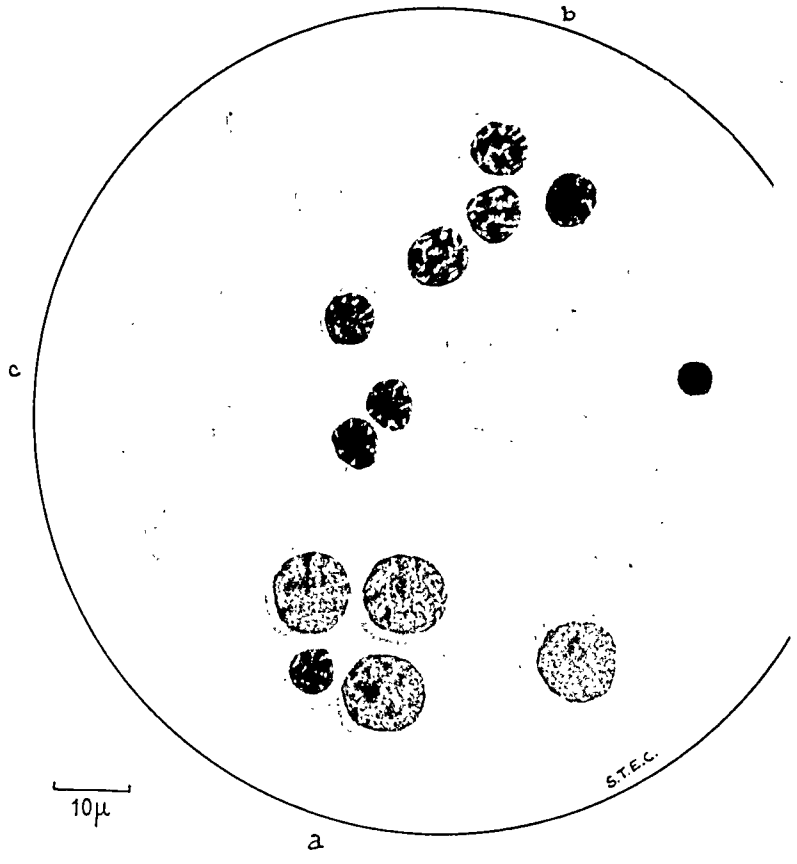


FIG. 6. (*a*) Early polychromatophilic erythroblasts. (*b*) Late polychromatophilic erythroblasts. (*c*) Orthochromatic erythroblasts. (Leishman stain)

Cells from sternal marrow showing early response to treatment (Case 21 (ii))

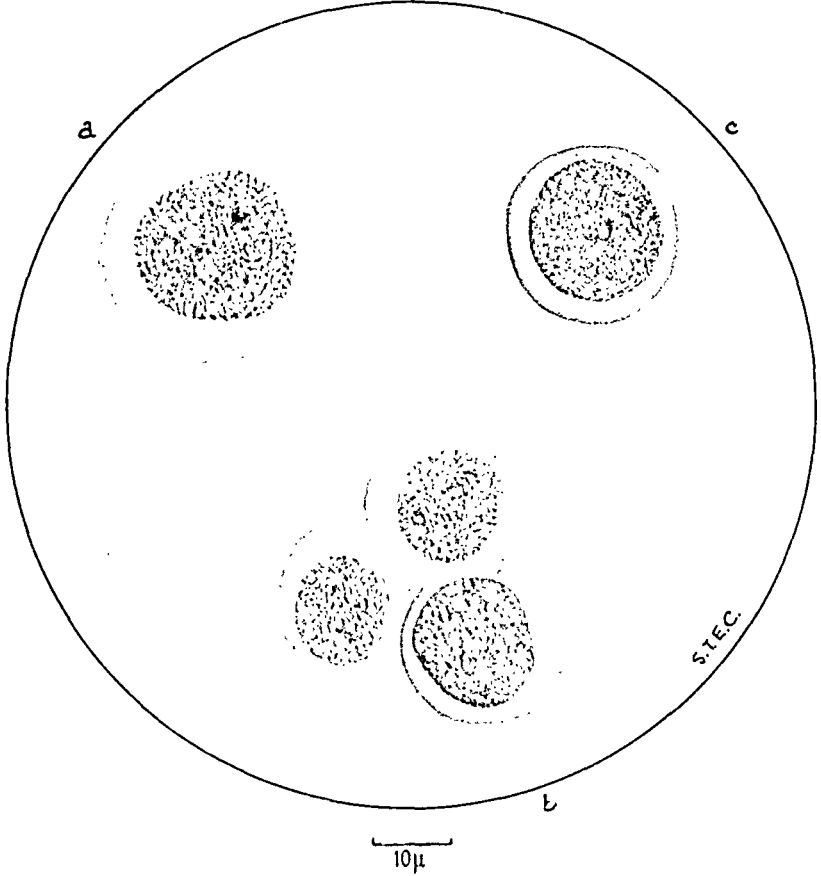


FIG. 3. Promegaloblasts. (*a*) Predominant type in this marrow with light blue cytoplasm. (*b*) Group showing traces of very early haemoglobinization. (*c*) More deeply basophilic promegaloblast. (Leishman stain)

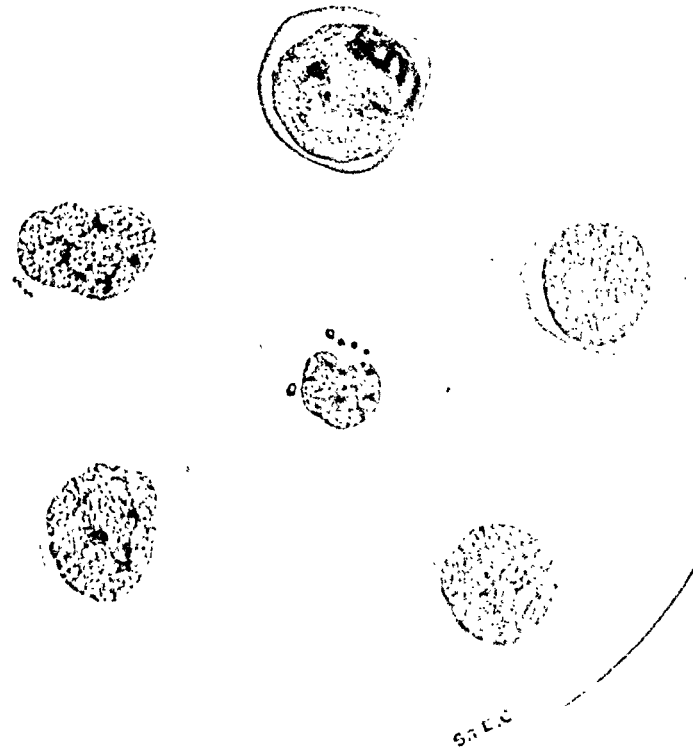
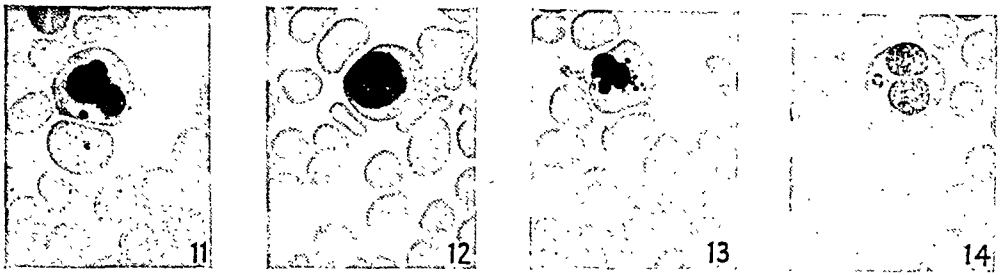
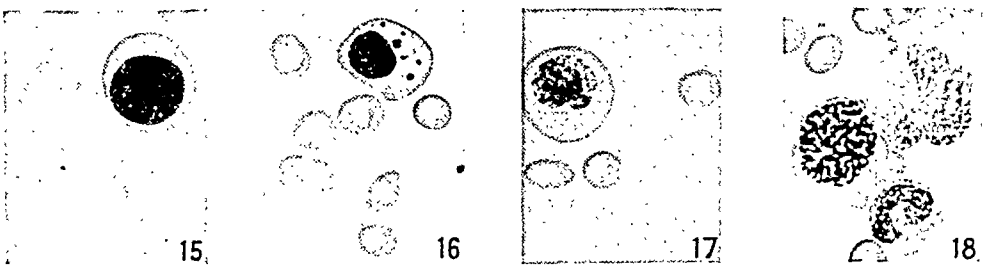


FIG. 4. Stages in the development of promegaloblast (*a*) to haemoglobinised megaloblast. (Leishman stain)

Cells from sternal marrow of an untreated Case of pernicious anaemia of pregnancy (Case 21 (ii))



FIGS. 11–14. Megaloblasts from peripheral blood films (× 700)
Left to right, Cases 17, 13, 13, and 11



FIGS. 15–16. Megaloblasts from peripheral blood films (× 700). Cases 15 and 16
FIG. 17. Haemoglobinized megaloblast from sternal marrow (× 700). Case 18
FIG. 18. Megaloblast in mitosis and pathological 'stab' cell from sternal marrow (× 700)
Case 21 (ii)

FIG. 19. Section of liver showing haemosiderosis (Prussian Blue reaction)
(Low-power magnification.) Case 23

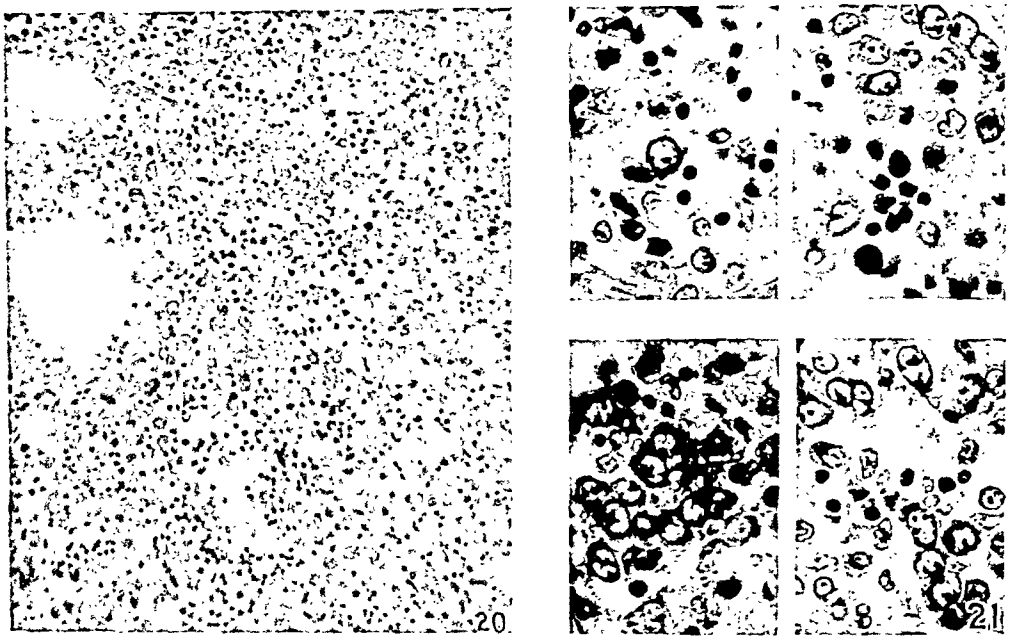


FIG. 20. Post-mortem section of femoral marrow showing extreme hyperplasia (×180). Case 23
FIG. 21. High-power views of the same marrow showing details of cells. Large masses of megaloblasts predominate (×500). Case 23

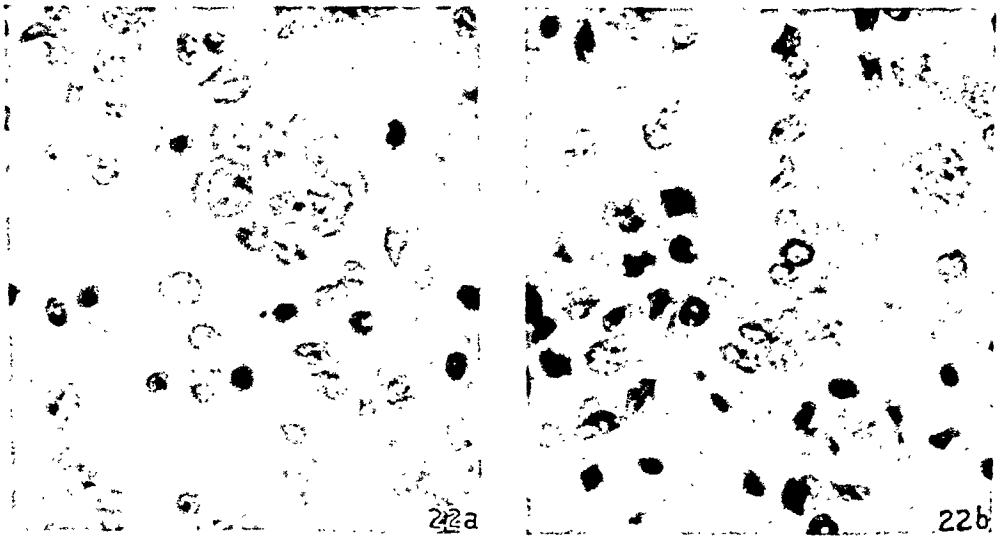


FIG. 22. Extramedullary haemopoiesis in the spleen. The cells lie within the sinusoids and resemble the primitive megaloblasts of the bone marrow (×1000). Case 23

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CYSTICERCOSIS (*Taenia solium*)

A FURTHER TEN YEARS' CLINICAL STUDY, COVERING 284 CASES[1]

By H. B. F. DIXON and W. H. HARGREAVES

With Plates 9 to 13

Introduction

Ten years have elapsed since MacArthur (1933) aroused widespread interest in the subject of cysticercosis when he published the results of his investigations on soldiers and ex-soldiers who had developed epilepsy during or after service abroad. Cysticercosis has since then come to be recognized as an important cause of fits occurring in persons who have been exposed to the risk of infestation. Dixon and Smithers, who were working with MacArthur at the Queen Alexandra Military Hospital, Millbank, published a series of 71 cases in 1934, including all cases recorded in the English literature since 1892, and a further series of six cases in 1935. Subsequently 22 British cases have been recorded by the following authors—Lindeman and Lyburn (1935), Dogra and Ahern (1935), Lipscomb (1935), Dick (1936), Howell (1936), Gottlieb (1936), Alexander (1937), Greig (1937, 1940), Evans (1938), Murgatroyd (1939), Brailsford (1941, 1942), Blyth (1941), Ewing (1941), Dickson and Willis (1941), and Ashton (1942). Altogether the cases recorded in the past 52 years number 99, of which 97 came from service personnel and their wives and families, the remaining two being missionaries. Since 1934 we have had the interesting experience of following up all of these patients who are still living, and in addition have collected a further 185 cases, bringing the total to 284. Many of these we have been able to examine personally at intervals, some have been seen by colleagues who have kindly sent us their reports, and we have followed up others by means of a written questionnaire.

Most authorities agree with MacArthur's (1933, 1937) conclusions regarding the pathogenesis of the disease, and we have little to add to them. As might be expected, however, in watching the natural history of cysticercosis unfold itself during this long period we have observed several interesting features which we consider worthy of publication. These features are concerned mainly with the aetiology, diagnosis, and prognosis of the disease. In our study of this large number of cases our observations regarding the prognosis have been the most interesting, and we hope to show that this is considerably better than has hitherto been thought. We have found in

[1] Received July 17, 1944.

searching for new cases that the incidence has not been as high as MacArthur expected. The number of cases discovered accidentally by radiographic examination has been small, although cysticercosis is now well known, and routine radiographic investigations for many and various reasons are carried out nowadays with increasing frequency. Again, in collecting these cases we have had access to the documents of pensioners, and cysticercosis causing disability in service men who have been stationed overseas is a pensionable condition. The various ex-service organizations are well aware of this, so that it is not likely that many cases which have been invalided from the Army have escaped us. On the other hand, in many cases the cerebral symptoms, if they exist, may be minimal or may be dismissed after clinical examination as being hysterical or vasovagal in origin. Often in our experience patients have borne such labels before the establishment of the correct diagnosis. In other cases the disability caused by the symptoms may not be found to warrant invaliding from the Army, but merely lowering of the medical category, so there are no records of them at the Royal Hospital, Chelsea. In this connexion it is significant to mention here that 19 of our 284 patients have never noticed any symptoms whatsoever. Finally, as MacArthur has pointed out, some patients who develop fits may hide their disability and deny it if questioned.

Aetiology

Considerable misconceptions still exist as to the methods of infestation. For example, in *Manson's Tropical Diseases* (Manson-Bahr, 1940) the surprising statement is made that 'it is possible that the infection is acquired in some way from pigs, either by eating sausages made from the intestines, or through some contamination by pig's excreta'. In view of this we feel justified in pointing out once again that the pig is the normal intermediate host of *Taenia solium*, becoming infested with cysticerci or larval forms of the tapeworm as a result of ingesting the ova which have been passed in human faeces. The adult tapeworm is found in man only, as the result of eating measly pork, and cysticercosis in man results from accidental infestation with the larval form. This is brought about either by the ingestion of food or drink contaminated directly by human faeces containing ova, or indirectly by flies, or by auto-infestation in the host of a tapeworm.

We have found that a striking number of patients give a positive history of tapeworm. Seventy-seven patients in our series of 284 gave such a history, and it is noteworthy that the cases with the heaviest degree of infestation radiographically—and some were found to be harbouring thousands of cysts—were among these. Incidentally, a negative history as regards tapeworm infestation is not always to be believed. Hurst and Robb-Smith (1942) illustrated this point when they described the case of a woman of 52 years who harboured *Taenia saginata* for some 25 years without noticing segments in her stools. Whether or not auto-infestation can take place, as we think possible, as the result of the regurgitation of ripe proglottides from

the small intestine into the stomach, there can surely be no doubt that, as in enterobiasis, a person harbouring a worm may convey ova to his mouth by his hands.

In the present series of cases there are a soldier's wife and daughter who both have heavy infestation radiographically. They have both been to India, and they both had tapeworms in Meerut in 1923. The daughter had one epileptiform fit whilst harbouring the worm in 1923, developed papill-oedema and optic atrophy and is now completely blind. The mother noticed transient nodules under the skin for some years after having the tapeworm, and suffered from fits from 1932 to 1935. The cases were discovered accidentally by Brailsford in 1941 as the result of X-ray examination of the mother for another condition. We consider that these are examples of auto-infestation, although admittedly it might be argued that these two persons may have contaminated one another.

Places of infestation. Of the present series 274 were undoubtedly infested in India, and the names of certain stations in India recur with striking regularity in the case histories. From a study of these, infestation appears to have occurred most commonly in Lucknow, Secunderabad, Rawalpindi, Ambala, Bareilly, Jubblepore, Cawnpore, Meerut, Fyzabad, Multan, Allahabad, and Ferozepore. Incidentally, these places are found to correspond to those where infestation occurred in the actual tapeworm cases. Only 10 of the patients had never been to India. Three of these had been to South Africa, two to China, two to Egypt, and one to Bermuda. Two had never been outside the British Isles. One was a woman aged 68 years, who had lived all her life in Kent and Surrey, and in whom cysticercosis was discovered accidentally at a radiographic examination. She had never had a fit. The other was an Irish Guardsman, who developed fits in 1933 and was diagnosed radiographically in 1934, when he was invalided from the Army.

Rank incidence. Of the 284 cases, 269 were soldiers or ex-soldiers, 11 occurred amongst the families of soldiers, including five children, one was a naval case, two were in the Royal Air Force, and two were civilians. Only nine of all the patients were female. There was only one officer patient in the series, and only four sergeants who held that rank at the probable time of infestation. The rest of the Army cases were corporals and privates. This rank incidence suggests that the better the living and eating conditions of soldiers the less is their chance of infestation. It is interesting to note that the officer patient and two of the sergeants gave a history of having had a tapeworm. The officer was invalided in 1938 on account of fits, biopsy of a solitary subcutaneous nodule was positive, and subsequent radiographic searches have revealed calcifying cysticerci in the skeletal muscles. His fits are now very infrequent. Since being invalided he has read for the Bar and is now practising his new profession successfully.

Regimental incidence. Comment on this may seem at first to be superfluous, but we have found that the incidence of cysticercosis has been particularly heavy in certain regiments of the Army. Thus the regiment in

which a suspected military case has served may prove to be a useful diagnostic point. Twenty-five per cent. of the patients while in India had served in the Royal Artillery or Cavalry. The infantry regiments in which most cases were found to occur were, in order of numbers of cases, Royal Berkshire Regt., Highland Light Infantry, Royal Fusiliers, Duke of Cornwall's Light Infantry, Worcestershire Regt., East Surrey Regt., Northumberland Fusiliers, Lincolnshire Regt., King's Royal Rifle Corps, the Buffs, Essex Regt., King's Own Regiment, North Stafford Regt., and Northamptonshire Regt.

Occupational incidence. Thirty per cent. of the Army cases had been either cooks or bandsmen. Bandsmen have more opportunities for visiting eating-places outside barracks and thus may meet greater risks of infestation than other tradesmen in the Army. Cooks may possibly have been infested by handling vegetables contaminated by ova of *Taenia solium*.

Diagnosis

A history of 'fits' of any description, varying from transient bouts of localized paraesthesiae and minor attacks possibly suggestive of *petit mal* to severe major epileptiform convulsions, after residence abroad, particularly in India, must bring to mind the possibility of cysticercosis. If the patient has been in one of the localities mentioned, and if there is a history of tapeworm infestation or contact with an infested person, this possibility becomes stronger, and particularly so if the patient was serving in the Army in India as a private or junior N.C.O. in one of the regiments which we have listed.

Nervous manifestations. MacArthur gave a complete description of these, but we have found that it is not generally realized how varied they may be. Epileptiform attacks of Jacksonian type are well recognized, but we wish to stress again the fact that minor symptoms are extremely common. In many cases in which we have established a positive diagnosis we have elicited symptoms to which little attention had been paid at the time and which had been forgotten. Cysticerci disseminated throughout the brain may produce any variety of focal symptoms, motor, sensory, or mental, with the resulting classical features of any focal lesion, and various focal symptoms may occur in the same patient. Commonly elicited histories are those of transient monoplegias, paraesthesiae, localized anaesthesia, visual and aural symptoms, aphasia, and amnesia. Many patients give a history of bouts of cramp in a limb lasting from 10 to 30 min. which may be preceded or followed by twitching or muscular spasm, and may sometimes lead on to a major attack with loss of consciousness. Major convulsions may occur without loss of consciousness, but bouts of unconsciousness without convulsions or any focal symptoms may be the only manifestation of the disease. An amazing variety of symptoms occurred in the following illustrative case.

Miss K., daughter of a Quartermaster in the Royal Signals, went to India (Rawalpindi) with her father in 1930 at the age of 10 years. There was no history of tapeworm or nodules. In 1931 she began to have momentary attacks in which zigzags of brilliant colours flashed in front of her eyes, followed by headaches and sometimes nausea and vomiting. At about the same time there was onset of occasional bouts of numbness and pricking in the right foot lasting a few minutes, 'as though something were inside my foot and trying to get out'. She returned to England in 1932 and a year later, when playing hockey, kept falling to the ground and developed spasmodic jerking of all the limbs, followed by weakness of the legs lasting about 15 min. and later a bursting sensation in the head. In 1934 an attack occurred in which her eyes, and later her head, jerked to the right. This was followed by numbness in the right foot which gradually spread over the right side of the body, including the face. She made queer noises, was unable to speak for 10 min., and for several hours was unable to articulate properly. One month later the same symptoms recurred, but this time were followed by numbness starting in the left foot also and spreading over the left half of the body. During the following year she had several minor attacks starting with numbness of the tongue and a dragging sensation at the back of the throat, followed by numbness beginning in the left thumb and left eye and spreading over the left arm and left side of the face, where muscular twitching occurred. These bouts lasted about 10 min. In June 1936, at the age of 16 years, she suddenly lost consciousness for the first time. This lasted some two hours, after which there was loss of memory for a day, during which she was unable to speak. One month later another attack occurred, starting with numbness in the left thumb and left eye which spread over the whole body. Her limbs jerked, she became speechless, and lost consciousness for five minutes. She bit her tongue during this attack, which was followed by a bursting sensation in the head lasting several hours. Another similar attack occurred one month later in a cinema, followed by loss of memory for one day. In December 1936, her vision began to fail and she was admitted to hospital. Marked papilloedema was found and cysticercosis was diagnosed radiographically; numerous calcified cysts were seen in the brain and skeletal muscles. The papilloedema increased, and a simple decompression was done in the hope of saving her sight. No superficial cysticerci were seen in the brain at the operation, after which her vision recovered and the papilloedema subsided completely in two months. After this, both major and minor attacks continued to recur, but gradually became less frequent and less severe. In 1940 she married and subsequently bore a healthy child. She is now practically free from symptoms apart from occasional migrainous attacks.

Mental symptoms. As might be expected, major epileptiform convulsions accompanied by loss of consciousness are usually followed by temporary affections of the mental state of varying duration and severity, in which the patient is dazed and irritable with impaired consciousness. Post-epileptic automatism is a possible feature which must be borne in mind. Tidy (1944) has told us of a soldier who committed a murder. He denied any knowledge of the crime, stating that he had had a 'black-out' at the time. His wife appealed on his behalf, and said that since returning home from service in India he had had occasional fits after which he often had violent outbursts of temper and performed irresponsible actions. On investigation he was

found to be suffering from cysticercosis, and subsequently was pronounced guilty but insane. It must be stressed that alterations in personality and disorders of behaviour may occur in cysticercosis with or without major or minor epileptiform attacks. The possibility of cysticercosis should be considered before a soldier who develops such symptoms after service in India is invalided on purely psychiatric grounds. Ten of our patients had previously been diagnosed as 'psychopathic personality', 'temperamental instability', or 'anxiety state'. A study of their documents showed that they had been first-class soldiers with exemplary characters prior to their return from India or their transfer to the Reserve before the war. One of these patients had been invalided from the Army in 1942 with a diagnosis of 'temperamental instability characterized particularly by a schizoid personality'. He gave a history of service in India from 1933 to 1938, and complained of persistent headaches since 1940 with bouts of depression, insomnia, lack of concentration, loss of libido, visual hallucinations at night, and impulses to do 'mad things', for example, 'to take a motor-cycle standing at the side of the road and drive like mad' or to attack and even kill people for whom he had conceived a dislike. After his discharge from the Army he was investigated further on the question of the attributability of his disability to service. On examining his Medical History Sheet it was found that in 1937 in India a nodule was excised from his chest wall and found on section to be a *Cysticercus cellulosae*. His diagnosis was altered to 'cysticercosis' and he was granted a disability pension. Our observations have not borne out the view of MacArthur, who believed that the general tendency in cysticercosis was one of retrogression, as evidenced by signs of mental deterioration which might be so marked as to necessitate institutional segregation. In fact only 14, or 5 per cent., of the 284 patients showed evidence of marked mental deterioration. In this connexion, Brailsford (1941), keeping a look-out for cases of cysticercosis, found no evidence of it in the radiographs of the patients at the Birmingham Mental Hospitals during a period of 20 years.

Methods by which the diagnosis was established. In the 284 cases the diagnosis was made in the first place in the following ways:

Biopsy of cyst	55
Biopsy and radiography	24
Radiography alone	188
An exploratory operation on the brain	5
An operation on the eye	1
At post-mortem examination	11
Total	284

Biopsy. A careful search for nodules by inspection and palpation of the whole body is the first step towards diagnosis. There was a history of transient nodules under the skin in 165 of our patients. In five cases cysts appeared in the tongue, in six they occurred in the eye, causing retinal detachment, and in three they were found in the heart at post-mortem examination. Living cysticerci are soft and impalpable in the tissues, and

their natural function is to remain alive in the flesh of their host, normally the pig, until ingested by man. When they die, they swell and become tense with fluid, and at this stage, which is followed later by shrinking and calcification, they may become obvious under the skin of the forehead, chest, arms, abdomen, or legs, or they may become palpable in the muscles or subcutaneous tissues. There is considerable variation in the size of these nodules; usually we have found them to be about the size of a small bean. The excision and examination of a suspicious nodule is obviously the most direct and definite method of diagnosis.

Radiographic examination. Of the cases, 188 were diagnosed originally by X-rays alone, and only 28 of these were discovered accidentally by radiographic examinations for some other purpose. The total number of cases in which the diagnosis was made radiographically came to 212, including the 24 with positive biopsies in addition. In a suspected case of cysticercosis, radiographic search of the whole body is indicated, starting with the limbs, because while heavily infested patients may show thousands of calcified cysts in the muscles, in some cases only a single calcified cyst may be found. Brailsford (1941) has stated that in suspected cases a radiograph should be taken either of the thigh or calf, and that if these fail to reveal calcified cysticerci, it is unlikely that radiographs of the skull will reveal them. We agree that radiographic examination of the skeletal muscles is more important, but it is interesting to note that 32 cases, more than 11 per cent. of the series, were reported as showing radiographic evidence of calcified cysts in the brain. In two of these skull X-rays alone were positive, a careful search of the general musculature being negative. We have come to the conclusion that if the radiographic appearances of calcified cysticerci in the brain were more widely known, more cases would be recognized. MacArthur (1933) noted that calcification in the brain, when it occurred, appeared to affect mainly the scolex, and found that 66 cerebral parasites out of 77 detected in films showed this scolex type of calcification, and quoted Morrison (1934) who worked with him, stating that the scolex as the solid part of the bladderworm might be expected to receive the main deposit of calcium, and that calcification occurred in the cyst wall, appearing as a definite halo. Brailsford (1941, 1942), on the other hand, has stated that the scolex can be seen as an area of relative transparency within the cyst, and that in his opinion the radiographic appearances are due solely to the deposition of calcium, first within the fluid contents of the cyst and later in the degenerated remains of the parasite, and that ultimately some calcium may be deposited in the cyst wall. Our study of radiographs of the skull has shown that the conclusions of MacArthur and Morrison are correct. Calcification most commonly appears in the scolex only, but quite frequently a calcified cyst wall may be seen like a shell or halo outside the scolex, and occasionally calcification can be seen starting in the cyst wall first. To demonstrate this, examples of calcified cerebral cysticerci are reproduced (Plates 9 and 10, Figs. 1 to 3). We have not seen the scolex as an area of

relative transparency. We find that high penetration, rather than the slight under-exposure advocated by Morrison, is effective in showing up the calcification in detail. Three of the five children in our series showed very well-marked calcification in the brain. We think that this is due both to the fact that calcification within the skull is more easily seen in children owing to the thinness of the vault, and to the increased activity of the calcium metabolism in childhood.

Cysticercosis with no palpable cysts and negative radiological findings. There is no difficulty in making the diagnosis in patients who exhibit cysts which can be excised for examination or are harbouring calcified cysticerci which can be shown radiographically, but cases may occur with typical histories in which careful clinical and radiographic examination prove entirely negative. We have followed up suspicious cases of this kind, examining them for nodules and X-raying them repeatedly at six-monthly intervals, and as a rule have been able to make a positive diagnosis eventually. From the point of view of the soldier who is invalided after service abroad on account of fits, a definite diagnosis of cysticercosis is obviously of extreme importance, as this determines the question of the attributability of his condition to military service and his right to a pension. We have met one outstanding example, which demonstrates how the disease may exist for years without any positive evidence, in spite of repeated investigations.

Pensioner T. N. R., late of the Royal Irish Fusiliers, went to India in 1929. In 1931, at the age of 20 years, he began to suffer from fits. There was no history of tapeworm, and he had never noticed any nodules under the skin. The fits were Jacksonian in character, being preceded by a flash of light and pain in the right side of the face. Numbness then occurred in the left leg and spread over the whole of the left side of the body. This was followed by loss of consciousness with twitching of the left arm and leg, lasting from 10 to 30 min. There was no incontinence of urine or tongue biting. After three fits in India, occurring at intervals from three to 11 months, he was invalided to England in October 1932.

He was investigated at the Queen Alexandra Military Hospital, Millbank, in February 1933 by one of us (H. B. F. D.). Physical examination was negative. The blood picture was normal, as also was the cerebrospinal fluid, and there was no eosinophilia. Radiographic examination of the skull and skeletal muscles showed no evidence of calcified cysts. Complement fixation and intradermal tests were negative. The faeces were normal, no ova or segments being found. In March 1933 he was invalided from the Army with the diagnosis of major epilepsy. The fits continued to occur as before, but repeated examinations at Millbank Hospital were persistently negative. In November 1936 he was admitted to the National Hospital, Queen Square. There again all investigations were negative, and in view of the fact that the attacks were local in origin it was decided to explore his brain. In January 1937 the leg area of the right motor cortex was exposed. The meninges were much thickened and a small hard nodule, about 4 mm. long, was removed from the cortex. On section and histological examination this was found to be a cysticercus of *Taenia solium*. Subsequently an application was made on his behalf for a disability pension, and a Medical Board was

held at the Queen Alexandra Military Hospital, Millbank, in June 1937. Cysticercosis was diagnosed and a 100 per cent. disability found.

He was last seen in 1943 prior to a Medical Board. Since the last operation there had been no change in the frequency or nature of the fits. He was an intelligent man and was running a small shop of his own successfully. His general condition was very good. The site of the decompression was satisfactory. No nodules were palpable, there were no abnormal physical signs in the central nervous system, and complete radiographic search of the skull and skeletal muscles once again revealed no evidence of calcified cysts.

This case illustrates how difficult it can sometimes be to establish a positive diagnosis of cysticercosis in spite of repeated careful examinations over the course of years. But for the findings on surgical exploration of the brain in 1937 this man would not be receiving a pension.

Cases subjected to cranial surgery. Including the patient just described, 14 of our series were operated upon. In five the diagnosis of cysticercosis had already been made, in five it was made at the operation, and four were not diagnosed in spite of exploration of the brain. As regards the five patients already diagnosed, in two decompression was performed to save sight, and this was effective, and in three an attempt was made to relieve fits by removing the offending cysticerci. One patient died after the operation, and the other two survived the operation, but continued to have fits as before. Here we must stress the fact that although strictly focal symptoms may be present, there are as a rule multiple cysts scattered throughout the brain, and incidentally the removal of the peccant cysticercus in the patient described above did not relieve his focal attacks. In none of our cases where cysticerci have been removed from the brain has the removal relieved the fits. It is noteworthy that 11 of these 14 patients presented symptoms of raised intracranial pressure with papilloedema. It appears to us that the only surgical operation justified is decompression in order to save sight. One other of these 14 patients is worth description.

Pensioner F. F., late of the Royal West Kent Regt., went to India in 1908 at the age of 21 years. He served there until 1915, when he went to Mesopotamia, whence he was invalided home in 1918 with malaria. Later that year he began to suffer from fits, both minor bouts of momentary loss of consciousness and major epileptic attacks, which were Jacksonian in character, starting with stiffness of the fingers of the left hand, followed by convulsive movements of the left arm and leg, then loss of consciousness lasting about 30 min., with occasional tongue-biting. These attacks occurred every few days, and early in 1919 he was invalided from the Army with a diagnosis of Jacksonian epilepsy, attributable to war service. Shortly after this he was admitted to the National Hospital, Queen Square, under Dr. Risien Russell, and on 23.3.19 Colonel Armour made an operative exploration of the right supramarginal gyrus and excised a transparent cyst. On microscopic examination a 'characteristic hydatid scolex' was found. After this the fits continued as before for two years, then their frequency gradually diminished. His records at Queen Square were found by one of us in 1933 and he came to the Queen Alexandra Military Hospital, Millbank, for examination. No history of tapeworm could be elicited, but he remembered

that in 1918, before the fits started, he had noticed some small intermittent swellings under the skin of his arms. The Jacksonian attacks were still occurring at intervals of about six weeks. Apart from evidence of the extensive trephine, physical examination was negative, and complete radiographical examination revealed no evidence of calcified cysticerci. After this he was not examined until 1943, at the age of 55 years. In the 10 years which had elapsed there had been little change in the frequency of the attacks, but the fits themselves were less severe. They consisted of a sensation of stiffness in the left arm and leg followed by twitching of the left side of the body, lasting about half an hour. Loss of consciousness was less frequent during the attacks. Incontinence of urine sometimes occurred. He had noticed no more nodules. Routine physical examination was again negative. X-ray examination of the skeletal muscles was also negative, but in the brain numerous calcified cysticerci could be seen.

Here again we have a patient who would have remained undiagnosed for many years but for the cranial operation, although even then a diagnosis of hydatid disease was made. Eventually calcification appeared in the brain alone, although there is a history of nodules in the arms 26 years ago.

Eosinophilia. Continental workers have attached too much importance to eosinophilia of the blood, according to Gotor (1942). It was found only in approximately 10 per cent. of our cases. With regard to the cerebrospinal fluid, we agree with MacArthur that such deviations from the normal as may occur have no positive diagnostic significance, and the fluid usually remains unaffected even when gross cerebral involvement is present.

Complement fixation and skin reactions. We have nothing to add to MacArthur's conclusions regarding these tests. Although they have occasionally been positive in proved cases, negative results are valueless as they have been obtained frequently in very heavily infested patients. We have therefore ceased to use these tests.

Prodromata. It might be expected that at the time when heavy infestation of the tissues with larvae of *Taenia solium* takes place there would occur some general reaction on the part of the host. MacArthur drew attention to the fact that sometimes at about the period of invasion there is a history of illness of a vague nature. We have been struck by the frequency with which, at times and at stations at which the infestation might have been expected to have occurred, entries have been found in Medical History Sheets of soldiers suffering from cysticercosis indicating that vague symptoms have occurred, usually lasting a few days. Entries such as 'sandfly fever', 'headache', 'myalgia', 'P.U.O.', and 'clinical malaria' are examples. It is notorious in India that the label of sandfly fever is too often applied to cases of vague fever lasting a few days and really of unknown origin. In addition to these records we have sometimes elicited histories of transient rashes appearing either alone or concurrently with the other symptoms and suggesting allergic manifestations. Our 275th case serves to illustrate these points.

L.-Cpl. C. H. H., aged 30 years, of the Dorsetshire Regt., was found accidentally to be heavily infested with calcified cysticerci in the skeletal

muscles during radiographic examination of his urinary tract in March 1944. He had gone to India in 1933 at the age of 19 years. In 1935 he suddenly developed a generalized skin eruption resembling a syphilide and was admitted to Hospital for 17 days. A diagnosis of psoriasis was made, the blood Wassermann reaction being negative. Four weeks after he left hospital, when the rash was still present, he had a pyrexial bout lasting five days. Blood-culture and examinations for malarial parasites were negative, and sandfly fever was diagnosed. Several months later he began to notice lumps, which came and went for about a year, under the skin of his arms and legs. At the end of that time he noticed tapeworm segments in his stools and consulted a chemist, who gave him a box of 'hookworm pills'. He took these and got rid of a considerable length of tapeworm. Later in the same year he began to suffer from vague attacks of dizziness lasting a few minutes, during which he found difficulty in controlling his limbs and noticed blindness of the upper halves of both visual fields. Sometimes momentary 'black-outs' occurred during the attacks. In 1943 in Egypt, when working with a spanner under a lorry, he suddenly lost the power of his right hand which became stiff for about half an hour. He was subsequently admitted to hospital for observation and investigation for six weeks. His condition was diagnosed as hysteria and he states that he was ridiculed. He decided never to report sick on account of the attacks again, and this he has not done, although they have continued to occur every few days.

Incubation period. The time which elapses between infestation of the body with cysticerci and the onset of cerebral symptoms is extremely variable. MacArthur found difficulty in fixing the date of invasion. The 26 per cent. of our patients who gave a positive history of tapeworm have proved useful in this respect, and have also been pointers towards the various stations in India where infestation is most common. Thus in many cases with no history of tapeworm we have been able to estimate the probable times of infestation by studying their records of service. It must be mentioned here that 11 patients had fits for at least a year, in one instance four years, before segments of tapeworm were noticed in the stools. Some patients were in hospital undergoing treatment for epilepsy when tapeworms were found; others had their first fit when in hospital under treatment for *Taenia solium* infestation. Some patients had their first fits within a few months of arriving in India. One soldier was treated for *Taenia solium* in Meerut in April 1934. He developed fits with evidence of increasing intracranial pressure and died after a cerebral decompression in September 1934; 200 cysticerci were counted in his brain at post-mortem examination. We have found that the incubation period has varied from this short space of time up to about 20 years; one patient, who never had a tapeworm, had his first fit in 1933, 19 years after leaving India where he had served from 1911 to 1914 at Secunderabad. Cysticercosis was diagnosed radiographically in 1938. Another patient was treated for *Taenia solium* in 1923 at Meerut, left India in 1925, and had his first fit in 1940. He was examined in 1941, when calcified cysticerci were seen radiographically in the brain and skeletal muscles. An analysis of 180 cases with no history of tapeworm shows that

the average period intervening between the time of arrival in India and the first cerebral symptoms was approximately seven years. The time of appearance of nodules also varies greatly. Subcutaneous nodules appeared in some of the patients with tapeworms before segments were noticed in the stools, within a few months of arrival in India, and in others they did not appear for many years, in one case 12 years. As we have said, the nodules are usually transient, but sometimes may take years to shrink away. This is specially the case when they appear in the thin subcutaneous tissue over the forehead or shin. Although nodules are usually noticed before the onset of fits, they may not appear until some years afterwards.

Prognosis

MacArthur could not commit himself in the matter of the prognosis of the disease and considered that it was a matter of extreme difficulty, but he certainly painted a gloomy picture on the whole, considering that the general tendency was one of retrogression. He had observed four cases, however, where fits had ceased after a duration which ranged from a few months to 20 years. As the result of observing the present large series over the course of years we have been able to obtain a better idea of the outlook of the average case, which is most certainly brighter than MacArthur supposed. Undoubtedly the prognosis of individual cases is very difficult. Some, as we have shown, may never have any symptoms of the disease, some have only minor cerebral symptoms, whilst others have persistent major epileptiform convulsions and manifestations such as marked papilloedema, calling for surgical interference. The time of onset of the symptoms after infestation is far from constant, varying from several months to more than 10 years.

The mortality from cysticercosis in our series has been very low, only eight per cent., and we have seen improvement take place in patients whose outlook for years appeared to be hopeless. In 1938, for instance, we obtained an invalid-chair for an ex-soldier, who had had major epileptiform attacks almost daily for five years in spite of anti-convulsant drugs, and was then completely incapacitated between the attacks. The man is now much improved and able to fend for himself. Our findings as regards prognosis are tabulated below.

Patients still living

Worse	20
Unchanged	92
Improving	81
Symptom-free (three years or more)	33
Never any symptoms	15
Total	241

Patients who have died

Fits within three years of death	32
Fits ceased	7
Never any symptoms	4
Total	43

Duration of Nervous Symptoms in 5-yearly Periods

Progress	1 to 5 years	5 to 10 years	10 to 15 years	15 to 20 years	20 to 25 years	25 to 30 years	30 to 35 years	35 to 40 years	Total
Dead	17	11	6	3	1	—	—	1	39
Worse	2	3	9	4	—	1	1	—	20
Unchanged	26	27	24	11	1	—	2	1	92
Improving	11	35	16	11	4	—	3	1	81
Symptom-free for three years or more	18	6	6	3	—	—	—	—	33
Total	74	82	61	32	6	1	6	3	265

(The remaining 19 patients who brought the total to 284 never had symptoms.)

Patients who have died

Died from cysticercosis . . .	22
Died after operation . . .	4
Died from other causes . . .	17
Total	43

It appears from these figures that there is no particularly dangerous time, which MacArthur believed to be from the sixth to the eighth year. In fact, of the patients whose symptoms were of from five to 10 years' duration 45 per cent. were improving and 8 per cent. had become symptom-free for three years or more. It is certainly most encouraging to find that only 8 per cent. of the patients now living are showing any signs of deterioration, and thus that 92 per cent. are either unchanged, improving, or free from symptoms, the latter two groups together predominating—36 per cent. of the patients are showing improvement and 15 per cent. have now recovered. We have not found that anti-convulsant drugs have any effect upon the course of the disease, although they sometimes help to control the fits. Epanutin has proved to be of value in this respect.

Summary

1. A clinical study of 284 cases of cysticercosis during the past 10 years has brought to light various points of interest.

2. Auto-infestation seems to be a common occurrence, judging from the fact that 26 per cent. of patients gave a history of tapeworm infestation. A tapeworm may be harboured unnoticed for years.

3. We have described again the great variety of symptoms which may occur. Severe mental deterioration is unusual, but changes in personality and disorders of behaviour may occur with or without fits. In the case of a soldier who has served in India and whose records show that he has been an efficient soldier the occurrence of such symptoms should arouse suspicion. He should not be labelled with a purely psychiatric diagnosis until the possibility of cysticercosis has been excluded.

4. The diagnosis is not always straightforward. There may be no detectable cysts and no calcification demonstrable radiographically. The history is of first importance. Of our cases, 274 were undoubtedly infested in

It is noteworthy that two had never been outside the British Isles. Only nine were female. Five were children when infested. The stations in India where infestation has occurred most commonly have been enumerated and attention has been drawn to rank, regimental, and occupational incidence.

5. A man who has served in India and gives a suggestive history might well be given the benefit of the doubt, in spite of repeatedly negative clinical and radiographic investigations. An exploratory operation on the brain should not be necessary to prove his case in order that he should be granted a pension. As regards the curative value of neurosurgery, it must be stressed that although the cerebral symptoms may be purely local in character there are, as a rule, multiple cysts in the brain. In none of our cases where the cysticerci have been removed from the brain has the fits been relieved. We consider that the only indication for surgery is threatened blindness from gross papilloedema which calls for decompression.

6. Calcified cerebral cysticerci are not unusual, being reported in 11 per cent. of the series, and we are convinced that more would be detected if higher penetration were employed. Their typical radiographic appearances are described and illustrations are given proving that MacArthur's conceptions are correct.

7. The incubation period between infestation of the body and the occurrence of symptoms has been found to vary from a few months to some 20 years.

8. Lastly, we have shown that the prognosis in cysticercosis is considerably better than has been believed.

Our grateful acknowledgements are due to all the colleagues who have so generously referred patients to us or furnished us with their notes, to Lt.-Col. E. Samuel and Major R. B. Guyer for their aid in recent radiographic examinations, to Miss M. Jenkins for her careful work in collecting and analysing the statistics, and to Major-General A. G. Biggam, Sir Arthur Hurst, Brigadier George Riddoch, and Brigadier Hugh Cairns for their suggestions and constructive criticisms.

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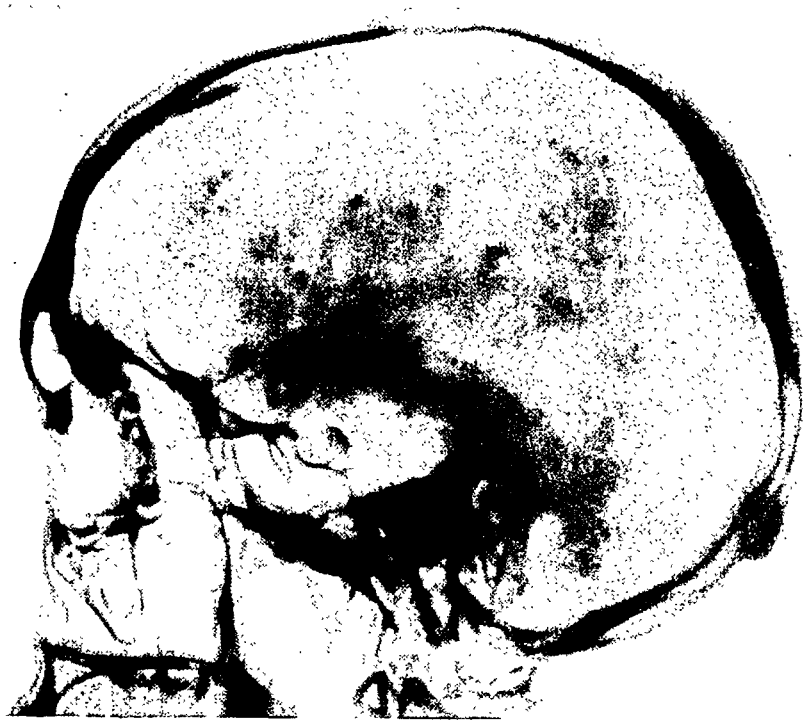

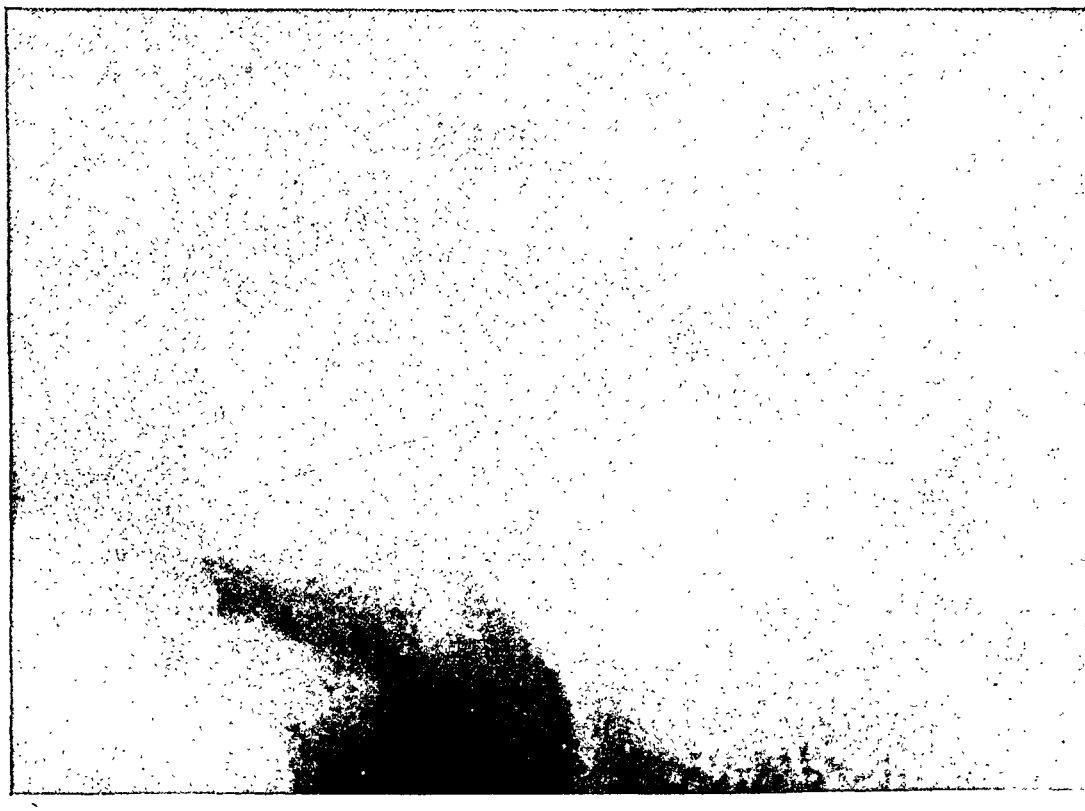

FIG. 1. *Calcified Cerebral Cysticerci.*

Pensioner A. V. K., aged 57 years. Served in India 1908 to 1919. History of contact with case of taeniasis in 1911. Onset of fits in 1917. Invalided in 1919 with diagnosis of epilepsy. Cysticercosis diagnosed radiographically in 1938. Fits now less frequent. Numerous calcified cysts in skeletal muscles and brain. Lateral view of skull, and enlargement, are shown. There is well-marked calcification in scolices and cyst walls.

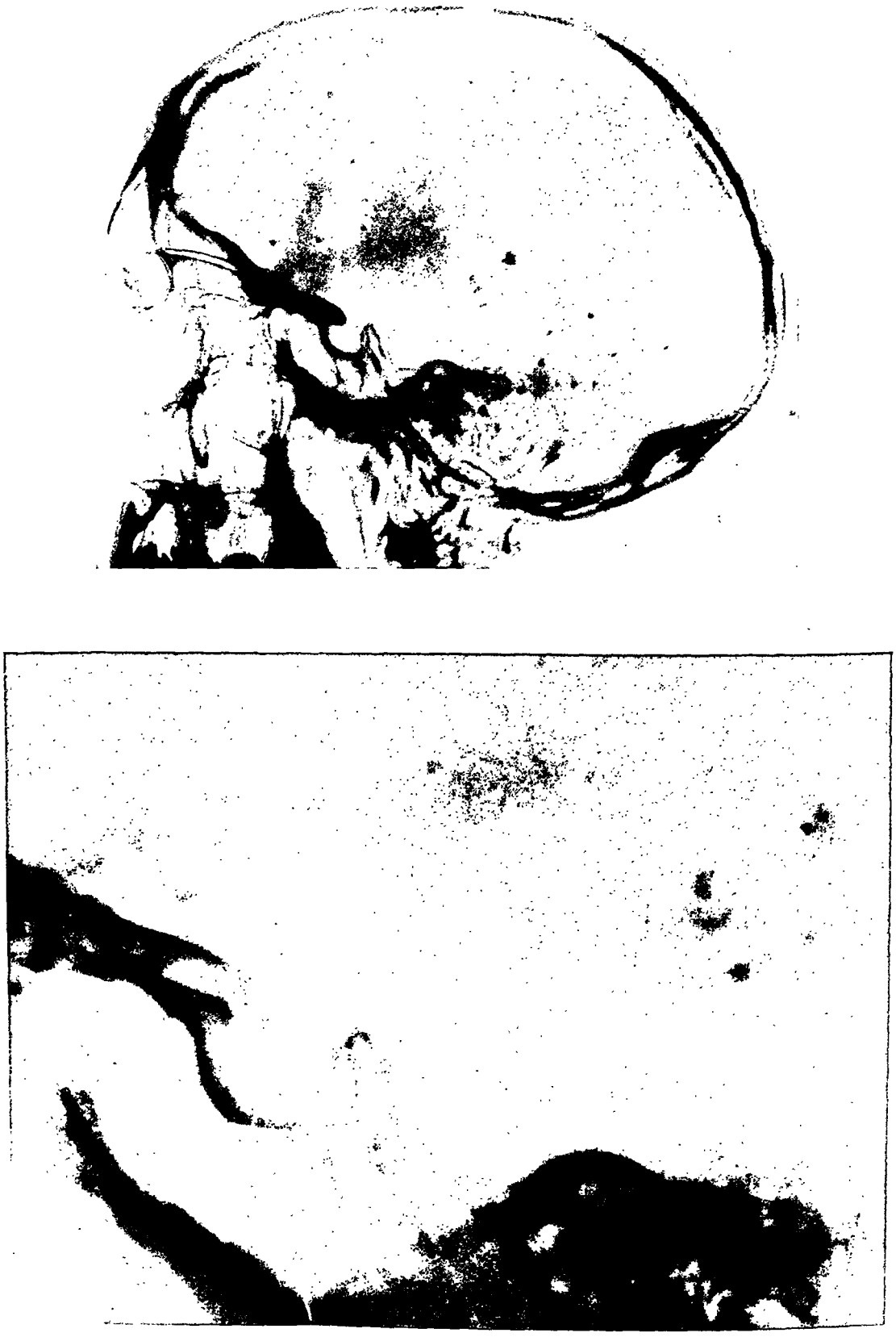

FIG. 2. *Calcified Cerebral Cysticerci.*

...er *J. C.*, aged 38 years. Served in India 1923 to 1929. Tapeworm in 1928. Fits started in same year, transient subcutaneous nodules which have continued. Cysticercosis diagnosed in 1934. Positive ...umerous calcified cysts ...

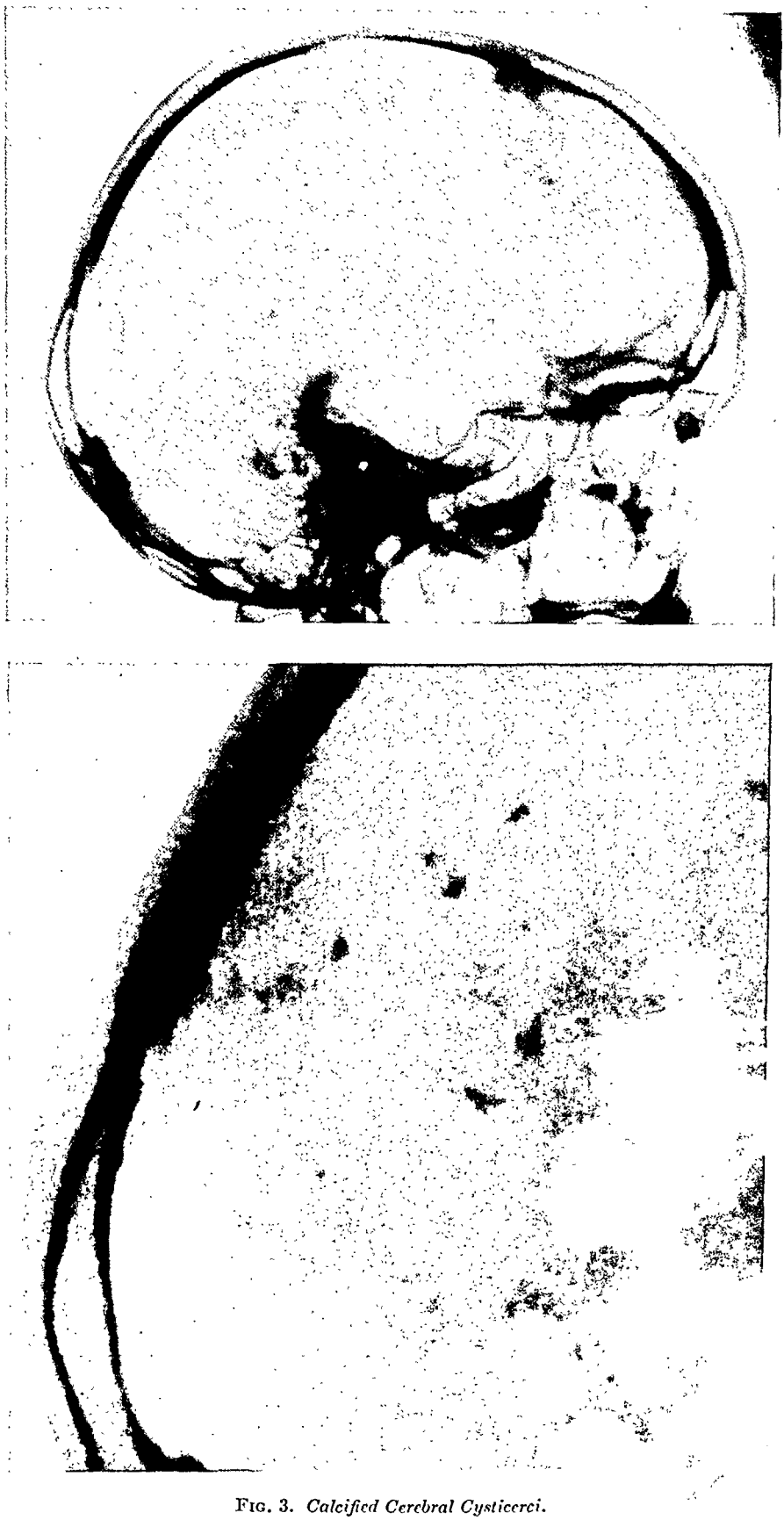

FIG. 3. *Calcified Cerebral Cysticerci.*

Craftsman J. B. C., aged 22 years. Son of a soldier. Brought up in In
1932. No history of tap Transient nodules and onset of fits in 19
12 years. Treated for i osy. Enlisted in 1943. Fits conti

FIG. 4. Antero-posterior view of skull of patient shown in Fig. 3.

FIG. 5. *Massive Infestation of Skeletal Muscles.* *Pensioner R. O.*, aged 56 years. Served in India 1908 to 1913. No tapeworm. Occasional transient nodules. Onset of fits in 1911. Invalided in 1915 with diagnosis of epilepsy. Cysticercosis diagnosed accidentally in 1934 when injured knee was X-rayed. On radiographic examination of the whole body over 3,000 calcified cysts were counted, a few being seen in the brain. Fits are becoming less frequent.

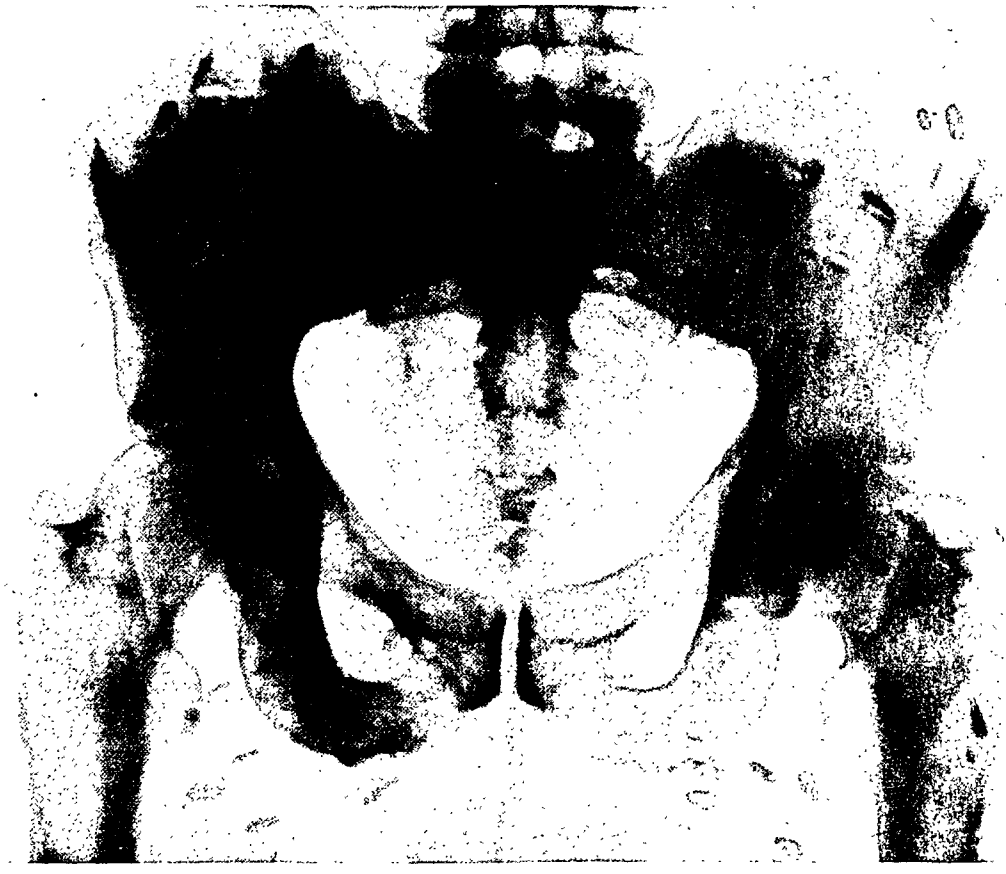

FIG. 6. *Large Calcified Cysticerci in Skeletal Muscles.*

Pensioner F. D., aged 42 years. Served in India 1922 to 1929. No history of tapeworm. No nodules noticed. Diagnosed radiographically in May 1942 during investigation for pain and stiffness in left leg. Epileptiform attacks started in September 1942 and have continued. Examined at the Queen Alexandra Military Hospital, Millbank, in 1943. Nodule palpable in right supraclavicular region. Numerous calcified cysticerci throughout skeletal muscles, but none in the brain. Large calcified cysts are seen, their long axes lying in the planes of the muscle fibres.

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THE ACTION OF INTRAVENOUS DIGOXIN IN MAN[1]

By J. McMICHAEL and E. P. SHARPEY-SCHAFER

(From the Department of Medicine, British Postgraduate Medical School, London)

Recent efforts to elucidate the problem of digitalis action (Fishberg, 1937; Harrison, 1939) seem to have made the subject still more incomprehensible. On the commonly held view that digitalis is a cardiac tonic, an increased cardiac output might have been demonstrable; the results obtained by the acetylene method have shown no consistency in this respect. Friedman, Clark, Resnik, and Harrison (1935) obtained very inconstant results, while Stewart, Deitrick, Crane, and Wheeler (1938) obtained evidence of an increased output only in cases of congestive failure, but the results of the latter workers were adversely criticized by Harrison (1939). Work on dogs showed that digitalis lowered the output of the normal heart (Harrison and Leonard, 1926). Dock and Tainter (1930) showed that digitalis lowered the venous pressure in dogs, an important observation since confirmed in normal man by Rytand (1933) and in cardiac patients by Stewart, Deitrick, Crane, and Wheeler (1938) and Wood (1940). The explanation of the fall of venous pressure in man has been left uncertain since Wood obtained evidence against the hepatic vein throttle mechanism suggested by Dock and Tainter.

The purpose of the present investigation was to obtain further information on cardiac output and right auricular pressure changes by the catheter technique of Cournand and Ranges (1941). Cardiac output changes can be followed serially and in rapid succession with considerable accuracy by this method.

Material and Methods

Twenty-five series of observations have been made on 24 subjects. Three were normal as regards the cardiovascular system, and the others suffered from some form and degree of heart failure (see Table I). The techniques of cardiac output (C.O.) and right auricular pressure (R.A.P.) estimation were essentially identical with those previously described (McMichael and Sharpey-Schafer, 1944); in patients with pulmonary congestion or pulmonary disease (for example emphysema) an arterial blood sample was taken as well to ensure an accurate figure for the arteriovenous oxygen difference. The R.A.P. is recorded in centimetres of saline above or below the sternal angle (normal supine −4 cm.). Digoxin was given through the catheter in doses of 1·5 mg. to secure a maximal effect, and observations were usually

[1] Received July 14, 1944.

TABLE I. *Data on the Effects of Intravenous Digoxin*

Case No.	Sex	Age	Diagnosis	R.A.P. cm. saline: Initial	R.A.P. cm. saline: Final	C.O. l. per min.: Initial	C.O. l. per min.: Final	Blood-pressure: Initial	Blood-pressure: Final	Heart-rate: Initial	Heart-rate: Final	Remarks
Group 1. Falling output:												
1	M.	49	Normal	−3	−5	4·5	4·1	114/62	124/64	88	84	Intermediate C.O. figures 4·3, 4·2
2	M.	36	Normal	−3	−6	6·7	5·2	135/80	125/75	56	52	(Fig. 1)
3	M.	69	Normal	−7	−9	4·0	3·3	146/90	146/80	80	76	
4	M.	66	Symptomless aortic stenosis	−8·5	−10	4·3	3·5	110/70	110/70	60	54	Intermediate C.O. 3·8
5	F.	59	Anaemia	4	0	9·5	7·8	116/60	130/60	140	136	Intermediate C.O. 9·1, 8·5
6	M.	61	'Cor pulmonale'	7·0	1·5	6·5	4·2	135/95	155/95	104	100	Arterial blood 76 % saturated with O_2
7	M.	50	'Cor pulmonale'	4	−1	7·7	6·0	132/85	126/70	96	92	Arterial blood 67 % saturated with O_2
Group 2. Rising output. Sinus rhythm:												
8	M.	36	Hypertension	20	15	3·8	5·0	245/150	—	120	120	
9	F.	49	Hypertension	8	4	3·1	3·4	255/160	—	104	100	Intermediate C.O. 3·2
10	M.	78	Old and recent coronary thromboses (P.M.)	25	21	4·3	5·1	80	76	76	76	Arterial blood 83 % saturated with O_2. Died 4 hours later
11	M.	64	Aortic stenosis. Failure	−2·5	−5·5	3·1	3·9	115/75	110/80	100	100	Mental confusion marked. Same patient as Case 23
12	M.	47	L. ventricular failure. Aortic incompetence	18	6	2·3	2·9	135/90	148/90	106	106	Gallop rhythm disappeared. Intermediate C.O. 2·6, 2·85
13	M.	61	Hypertensive heart failure	7	0	2·6	3·0	170/130	190/135	92	88	Arterial blood 87 % saturated with O_2. Also cuffs. (Fig. 2)
14	M.	43	Mitral and aortic stenosis	6·5	−1·5	2·9	4·15	95/60	95/60	104	98	Intermediate C.O. 3·25. Also cuffs. (Fig. 3)
15	F.	33	Mitral stenosis	21	11·5	2·45	3·15	94/80	126/90	124	120	Intermediate C.O. 2·7, 2·9. Cuffs. (Fig. 4)
16	M.	62	Hypertensive heart failure	8	0	3·05	5·3	200/130	200/134	105	134	Desire to micturate caused rise of rate. (Fig. 7)
17	F.	45	*Auricular fibrillation:* Thyrotoxicosis	32	17	3·04	5·55	120/80	120/80	190	130	V.P. fell gradually to 0 in a week, Hb. rising from 84 to 114 %. (Fig. 6)
18	M.	66	Hypertension	5	1·	4·62	5·03	190/95	—	84	78	
19	M.	49	Mitral stenosis and aortic incompetence	0	−4·5	3·85	5·76	170/70	—	86	64	Intermediate C.O. 4·2, 5·2
20	F.	54	Mitral stenosis	6	−3	2·5	3·3	95/—	130/—	160	115	Arterial O_2 88 %. Intermediate C.O. 2·85
21	F.	44	Mitral stenosis and aortic incompetence	7·5	−2·5	2·3	3·8	120/80	140/80	155	95	After 3 hr. C.O. 3·5
22	F.	55	Mitral stenosis and hypertension	17	11	2·8	3·6	190/90	210/85	130	86	Also cuffs. (Fig. 5)
Group 3. Output essentially unchanged:												
23	M.	64	Aortic stenosis	−4	−6	4·3	4·5	140/75	—	68	68	After recovery from acute L.V. failure. Same patient as Case 11
24	M.	39	Malignant hypertension	−8·5	−11·5	3·95	3·85	250/200	—	104	104	Intermediate C.O. 3·75, 3·85
25	F.	72	Thyrotoxicosis	12	7	2·7	2·9	120/80	125/90	134	134	Also cuffs. B.M.R. +40 %

carried through for an hour after injection. The fall in right auricular pressure was always complete well within this time, as was any change in heart-rate in patients with auricular fibrillation. As a control on the effects of digitalis lowering of venous pressure, pneumatic cuffs on the thighs at 80 to 90 mm. mercury were used to congest the legs, and thus produce

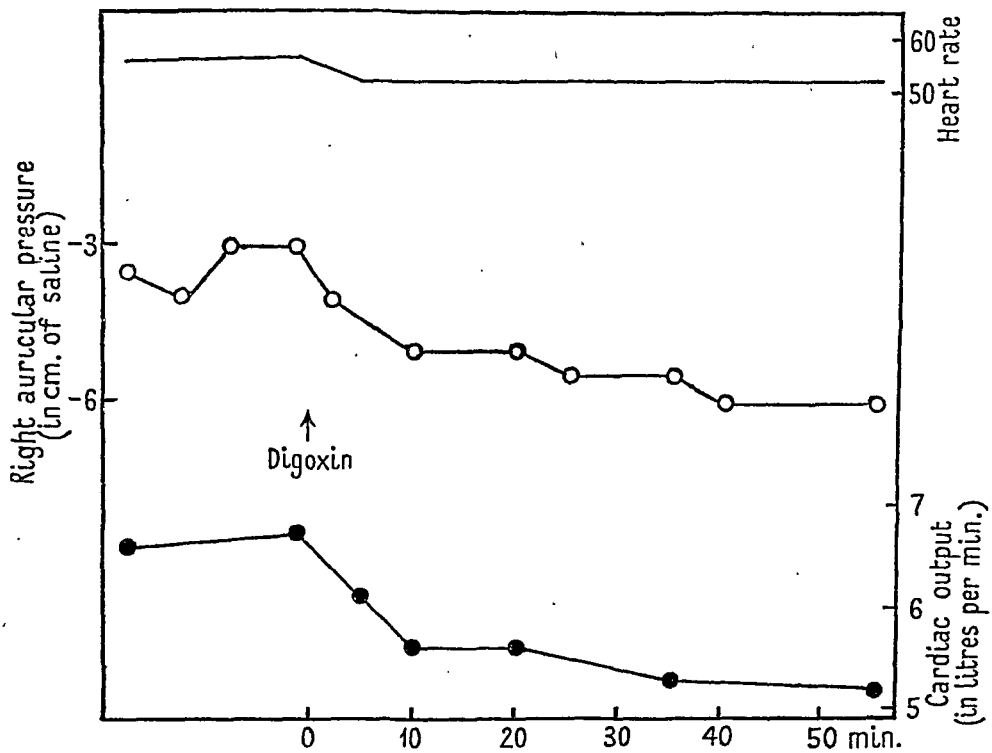

FIG. 1. Normal. Digoxin 1·5 mg. injected at the arrow. R.A.P. and C.O. fall in parallel.

a simple mechanical lowering of right auricular pressure (McMichael and Sharpey-Schafer, 1944).

In interpretation and tabulation of results the following criteria have been adopted. A change in cardiac output of 0·4 l. per min. or more is regarded as significant. Spontaneous fluctuations of this magnitude are not seen when a steady state of metabolism and pulse-rate are reached. In patients with congestive failure and a low cardiac output changes of this degree are even more significant than in normal subjects. Thus an increase of 0·5 l. in a normal subject with C.O. of 5 l. per min. represents a 10 per cent. change, while in a patient with an output of 2·5 l. per min. it signifies a 20 per cent. increase. If serial estimations show a steady upward or downward trend within the range of 0·4 l., the series is also regarded as unlikely to be fortuitous.

Results

The one constant effect of intravenous digoxin was a fall of right auricular pressure. Cardiac output was noted to rise in 15 observations, while in seven

it fell, and in three no significant alteration could be detected. The data in Table I make it clear that these types of cardiac output response have other associated features, justifying their separation into the following groups:

1. Those with an initial normal or high cardiac output where a fall in R.A.P. is accompanied by a fall in cardiac output.

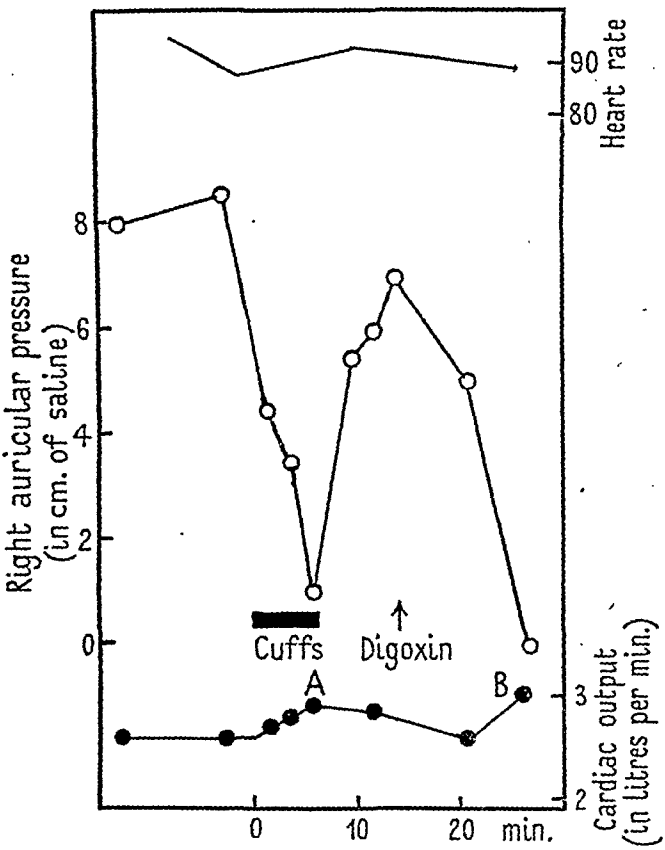

FIG. 2. Congestive failure. Lowering the R.A.P. by congesting cuffs on the legs leads to a slight but definite increase in cardiac output. A similar slight increase subsequently results from digoxin.

2. Those with an initial low output in which reduction of R.A.P. is accompanied by a rise in output.

3. In the intermediate group showing no change in output two cases will be shown to have features of 'early' or 'recovered' failure, while another seemed to be at an advanced or irresponsive stage.

Group 1. Falling output. This group is noted to include three normal subjects in whom a reduction of R.A.P. would in accordance with Starling's law be expected to lead to a fall in output of the heart (Starling, 1918; McMichael and Sharpey-Schafer, 1944). The degree of cardiac output change observed in these subjects is in complete conformity with expectation if the reduction of right auricular pressure is regarded as primary. The pathological instances include a case of anaemic heart failure in which the heart

output is high (Sharpey-Schafer, 1944). Two cases of *cor pulmonale* with high outputs also fall in this group. As regards available arterial oxygen, patients with *cor pulmonale* are in a plight similar to those with severe anaemia, and the cardiac output may be high for similar reasons. In all

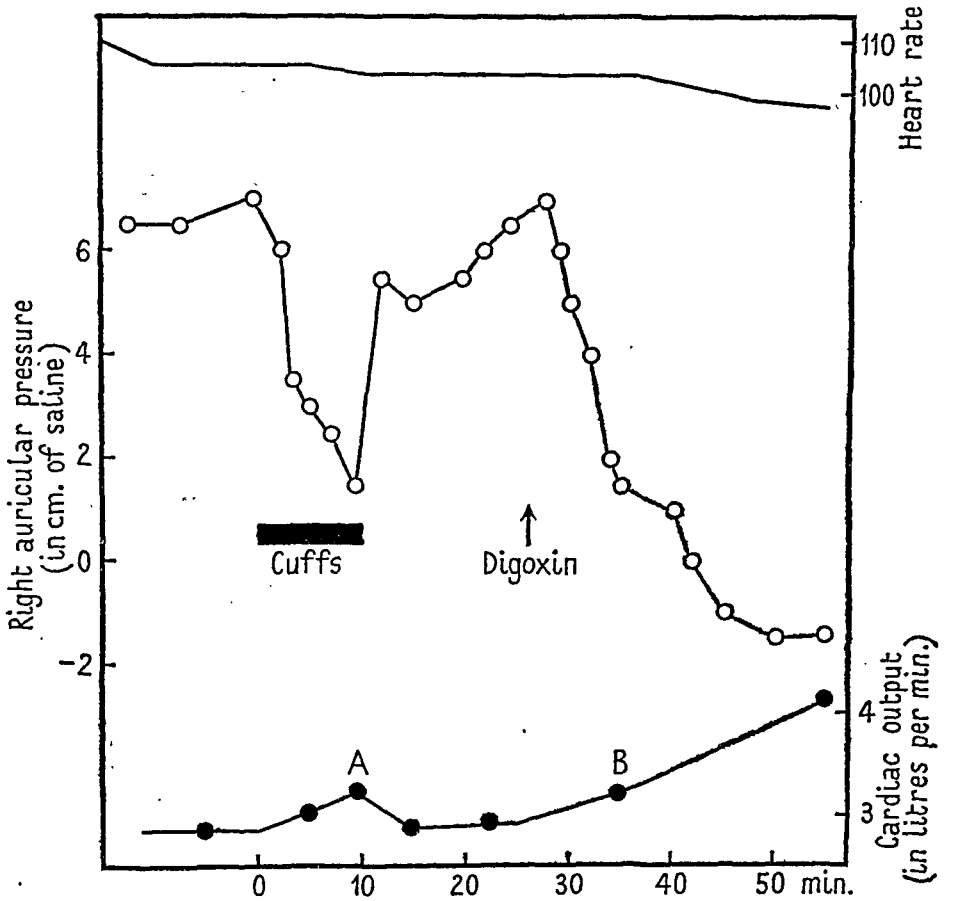

FIG. 3. Congestive failure. Lowering the R.A.P. leads to a slight increase in C.O. Digoxin produces the same effect at point B, but subsequently the effect on both R.A.P. and C.O. is much greater.

these instances, therefore, the heart is either normal or responding normally to venous pressure changes within the tested range, that is, output increases with a rise and decreases with a fall in venous pressure.

Group 2. Increasing output. This is the group of critical interest. All the patients suffered from heart failure with some degree of venous congestion. In accordance with current ideas on digitalis action, it would be easy to accept the interpretation that the increasing output is an indication of improvement of cardiac contractility from digitalis. In deciding this point it is necessary to study separately the cases with auricular fibrillation and those with sinus rhythm in which heart-rate effects could play little or no part.

Sinus rhythm. Four cases were subjected to control study by simple

mechanical lowering of venous pressure by pneumatic cuffs on the thighs. From previous data obtained by a less accurate method (McMichael, 1938) little change in cardiac output might have been expected from this procedure, and had the cardiac output shown a significant rise with digitalis,

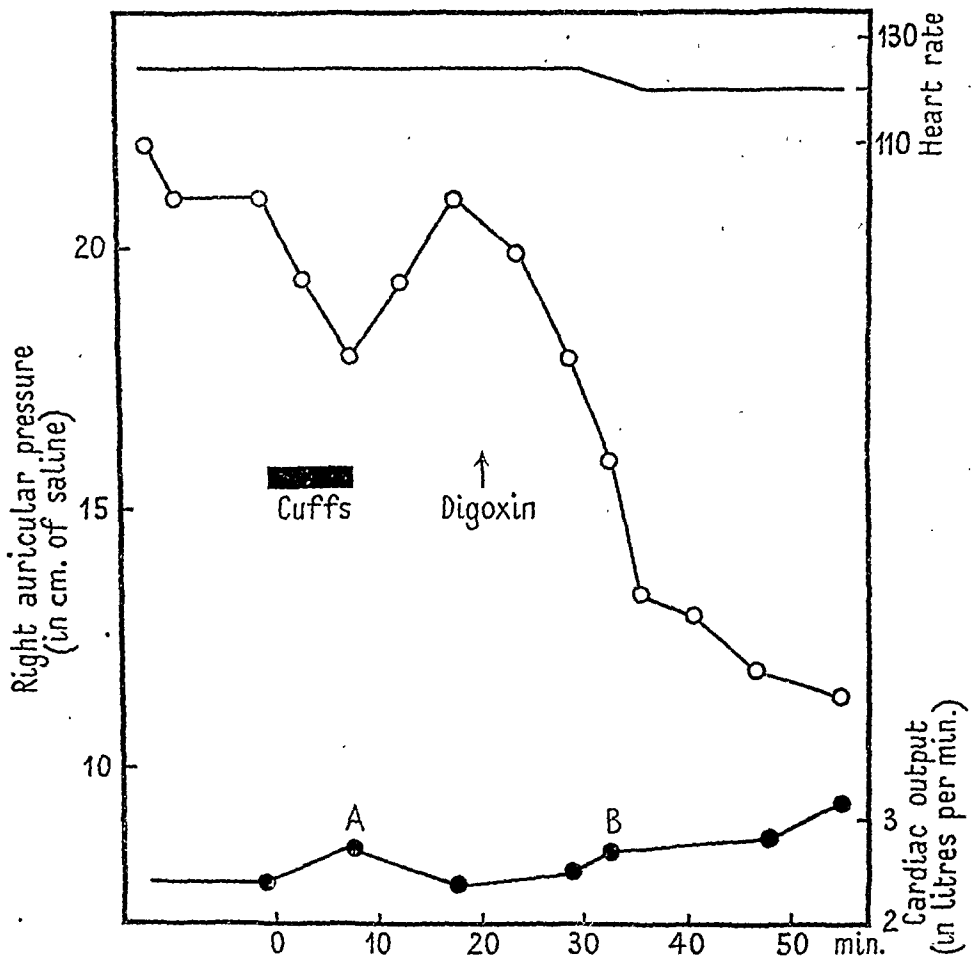

FIG. 4. Congestive failure. Mechanical lowering of R.A.P. and digoxin effects are similar at points A and B. Subsequently digoxin effects are more profound.

this could have been regarded as proof of increased cardiac efficiency resulting from a direct cardiac action of digitalis. We were surprised to find that in every instance simple mechanical lowering of the R.A.P. produced the same quantitative and qualitative change in cardiac output as a similar reduction of R.A.P. by digitalis. This is best seen in Fig. 2 where the mechanical and digitalis effects were nearly identical. In Figs. 3 and 4 the digitalis effect is more profound and of course more lasting than the mechanically produced venous pressure fall; comparison at the points A and B in the figures, however, indicates the close similarity of the responses at similar venous pressures.

Auricular fibrillation and rate control. In the series were six patients with auricular fibrillation. The response to digoxin was similar in degree to that observed in those with sinus rhythm. This similarity is seen in Table II.

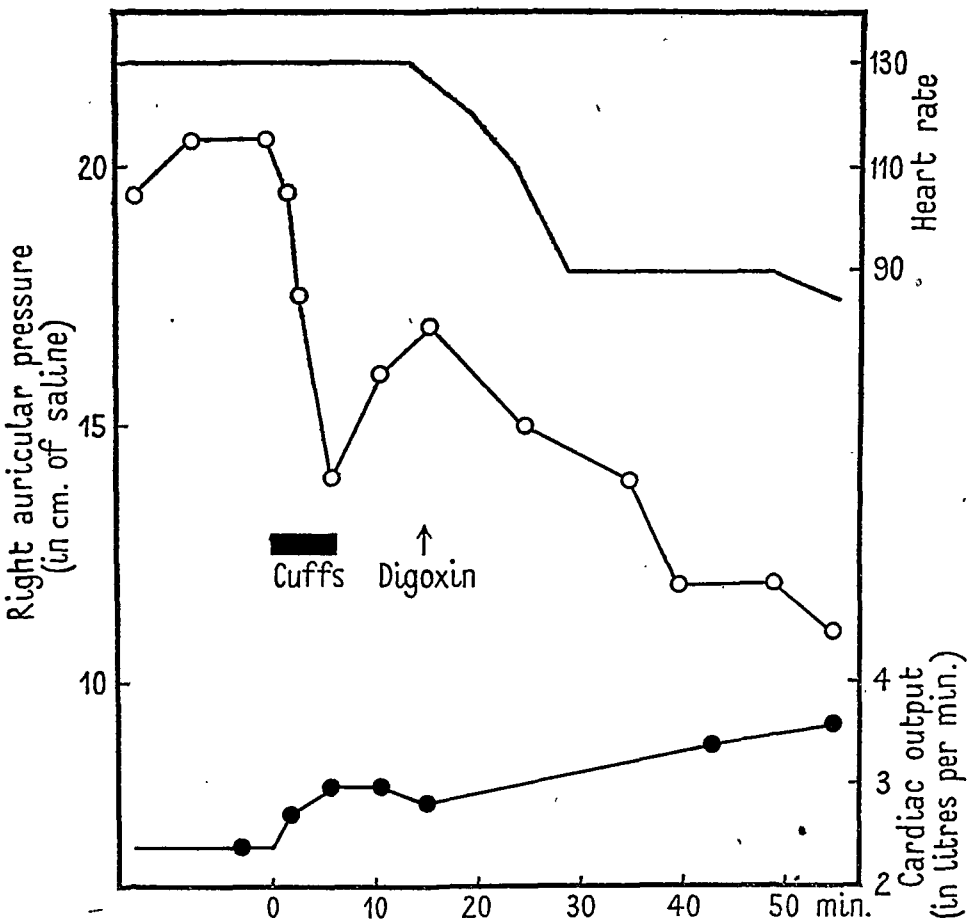

FIG. 5. Auricular fibrillation with congestion. Mechanical lowering of R.A.P. without rate control increases C.O. Digoxin subsequently produces proportionately greater effects on C.O. and R.A.P. Fall in heart-rate has little effect.

TABLE II

Digoxin increase in C.O. (l. per min.)	Number of cases	
	Sinus rhythm	Auricular fibrillation
Less than 0·5	2	1
0·5 to 1	4	2
1 to 2	2	2
2 to 2·5	1	1

In one case cuffs on the thighs reducing venous pressure without any rate control produced a 25 per cent. increase in cardiac output. Further reduction of venous pressure by digoxin produced only a further proportional increase in cardiac output, rate control from 130 to 86 apparently having little influence on the ultimate result (Fig. 5).

The cases with auricular fibrillation and sinus rhythm showing the most pronounced rises in output are worthy of comment. In the first, a case of

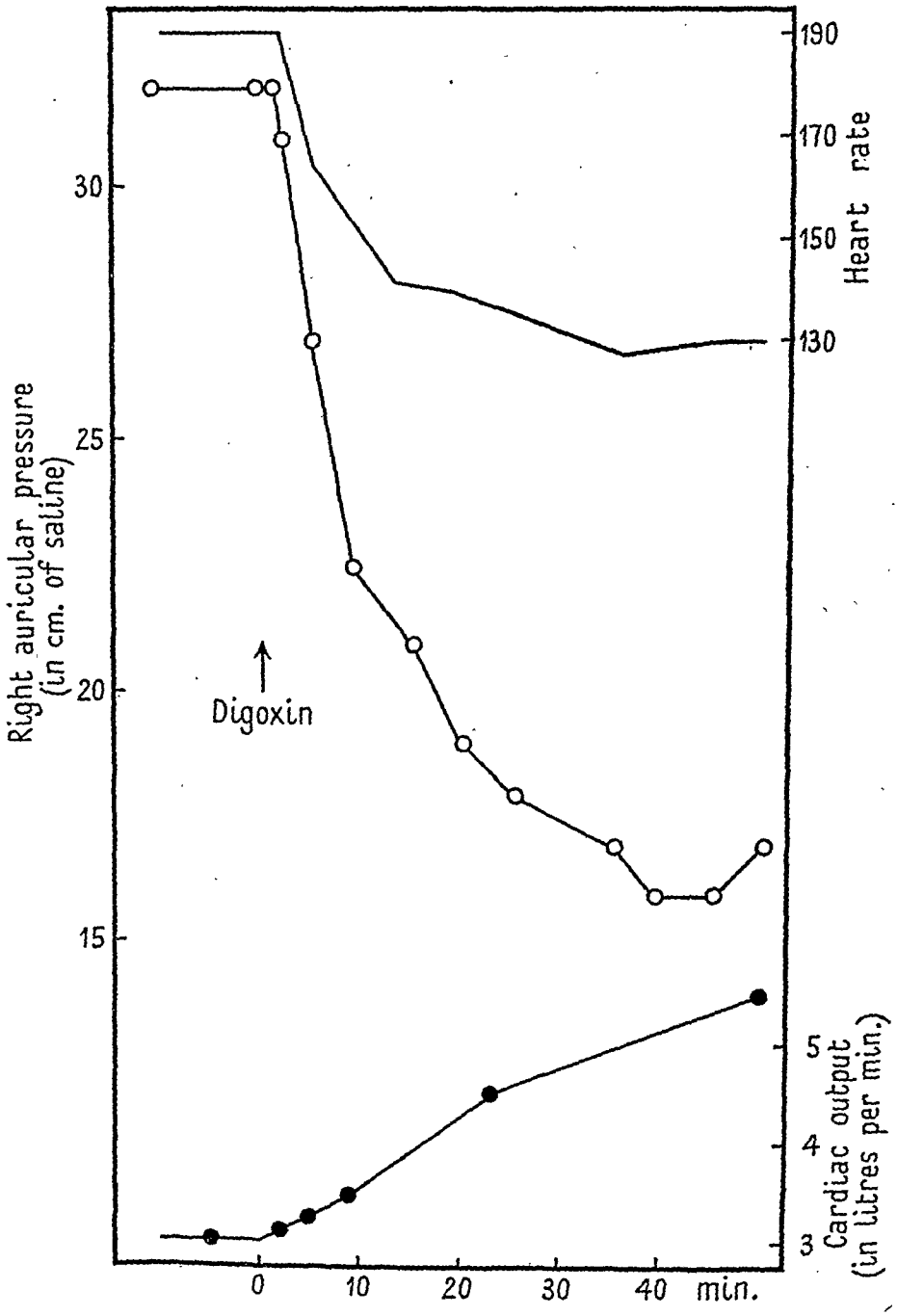

FIG. 6. Thyrotoxic fibrillation. A very pronounced increase in C.O. and fall in R.A.P. accompanies rate control (see text).

thyrotoxic fibrillation, the ventricular rate was unusually rapid. The venous pressure fell steeply with digoxin (Fig. 6), and then began to flatten in the last

30 min. of observation. During this latter period cardiac output continued to rise steadily, reaching a level 83 per cent. above its initial value. It might

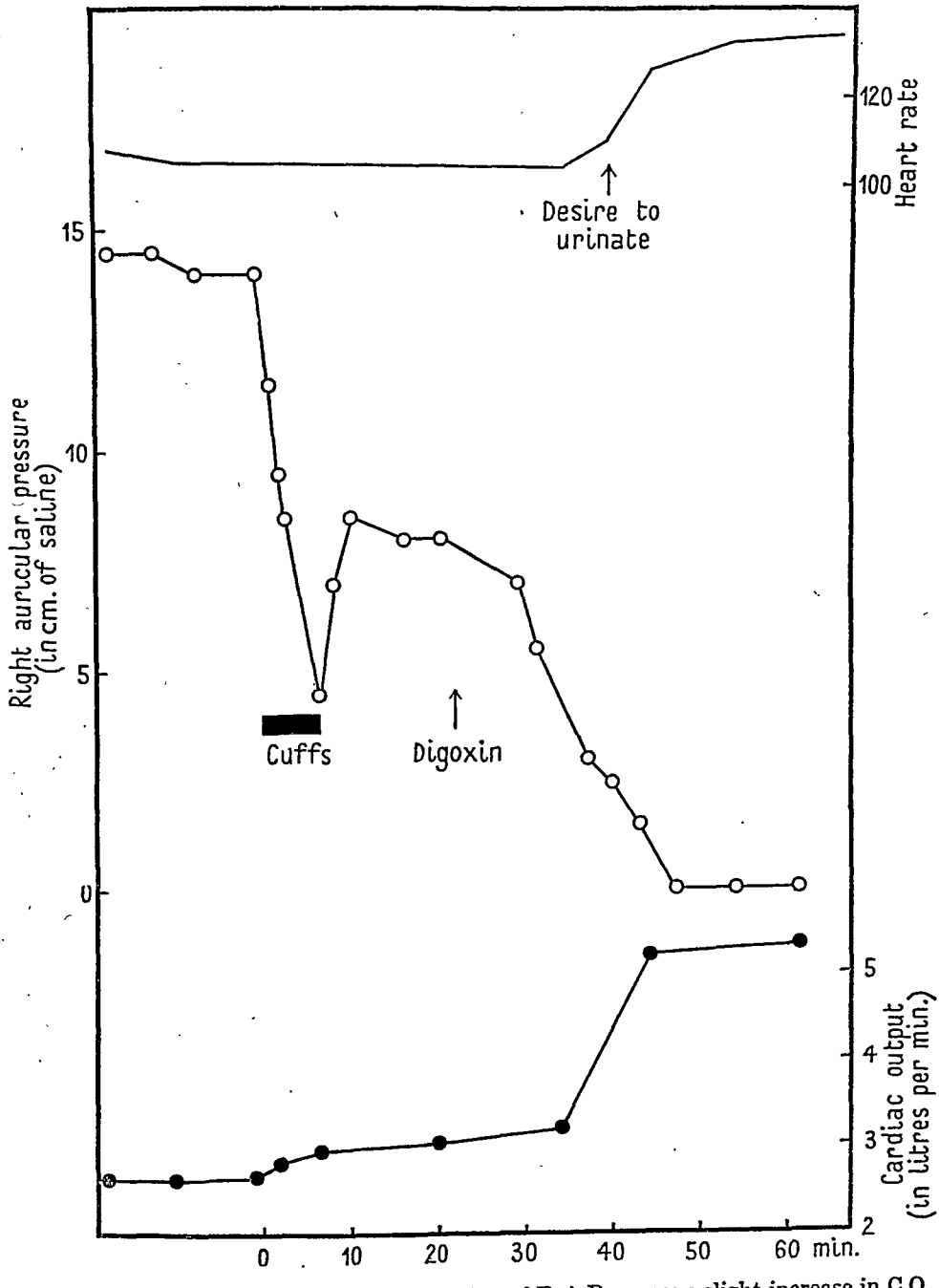

FIG. 7. Sinus rhythm. Mechanical lowering of R.A.P. causes a slight increase in C.O. Digoxin subsequently increases both effects to an unusual degree, unimpaired by cardio-acceleration.

reasonably have been assumed that rate control was playing a part in this progressive improvement. The case with sinus rhythm, however, indicates

that caution must be exercised in ascribing improvement to slowing (Fig. 7). It is seen that a late increase in heart-rate (associated with a distended bladder) was associated with a quite remarkable (100 per cent.) increase in cardiac output above the initial level. In a patient aged 60 years (not included in the tables) with symptomless auricular fibrillation and R.A.P. −5 cm., increasing the ventricular rate from 80 to 120 with atropine did not lead to any change in cardiac output, which remained 4·2 l. throughout; R.A.P. fell 1 cm. Further comparative work on a much larger series is required to settle whether heart-rate control has any demonstrable effect.

Group 3. Intermediate group with no significant cardiac output response. In the transition from normal reactions (Group 1) to congestive failure (Group 2) we encounter a group of cases with indeterminate cardiac output response to digoxin, although venous pressure is lowered as in the other two groups. The types encountered here include a patient with malignant hypertension who was just beginning to have attacks of nocturnal orthopnoea, but without systemic venous congestion. This might be regarded as 'early' failure. A second was a patient with calcareous aortic stenosis who had recovered from an attack of left ventricular failure 10 days previously. He showed no change in cardiac output after digoxin. The same patient in further left ventricular failure three months later showed a lower output and a slight but definite rise in output with digoxin (Group 2, Case 11). When digitalis produces no effect on cardiac output, mechanical lowering of venous pressure also produces no change. In Case 25 cuffs on the thighs reducing the R.A.P. from 12 to 5 cm. produced no significant change in cardiac output, which only fluctuated slightly between 2·6 and 2·8 l. per min. Failure in this case was extreme and led to a fatal termination four days after the observations were made.

Discussion

The most significant new fact which comes out of the above observations is that in congestive failure simple mechanical lowering of right auricular 'filling' pressure may be accompanied by an increase in cardiac output; hence the immediate effects of intravenous digoxin may be accounted for by a primary action of the drug on venous pressure. A tentative hypothesis to explain this observation is that the heart in failure behaves like the overloaded heart as shown by Starling (Fig. 8). As the venous pressure is increased a stage comes at which the curve of cardiac output response flattens and then begins to go down. If we imagine that in cardiac failure (Group 2 in the present paper) the heart is 'over the top' of the curve, a reduction in venous pressure might well be accompanied by an increase in output. This idea finds support in the existence of intermediate responses which fall on the flat part of the curve between the normal controls and the cases of severe congestive failure. It also fits in with the demonstration by Stewart, Deitrick, Crane, and Wheeler (1938) of reduction in cardiac size associated with the digitalis fall in venous pressure and increase in cardiac output.

Katz, Rodbard, Friend, and Rottersman (1938), impressed by the profound fall of venous pressure resulting from digitalis in the whole animal, raised the possibility that the action of digitalis in heart failure might be entirely accounted for by this peripheral action of the drug. This was followed up by a critical review and experimental analysis (Katz, Mendlowitz, and Kaplan, 1938) showing that digitalis had no direct effect on the contractile

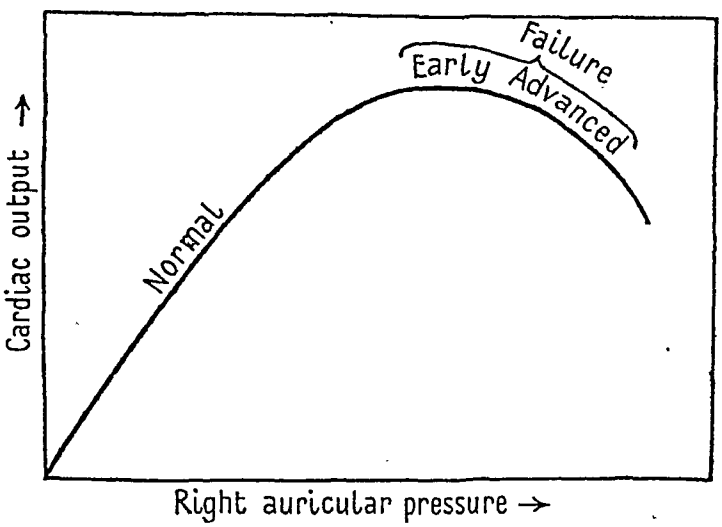

FIG. 8. Starling's curve. Increase of filling pressure is accompanied by an increase in output until the heart is overloaded; thereafter the output begins to fall with any further increase in pressure.

power of the isolated mammalian heart; the only direct effects of the drug consistently observed were ectopic rhythms and effects on conduction. Our work seems to lend support to this view.

Rate control. The emphasis laid by some cardiologists (Mackenzie, 1925; Lewis, 1937) on the therapeutic influence of rate control of fibrillation has often been questioned on clinical grounds (Christian, 1919; Gavey and Parkinson, 1939). The above findings show quite clearly that the beneficial effects of digitalis are in the main due to a primary relief of venous engorgement, the fall of venous pressure and increase in cardiac output being similar in degree in patients with sinus rhythm and auricular fibrillation. Rate control may play a secondary part, but quantitatively a difference is not obvious in these few short-term observations. It is of course possible that there is a long-term beneficial effect from the reduction of the energy wastage in ineffectual beats, not demonstrable by this type of experiment.

The cause of reduction in venous pressure is still obscure. It has certainly nothing to do with increasing cardiac output, as it also occurs in cases showing no change or a fall in output. The suggestion of Dock and Tainter (1930) that the liver and portal system became congested has been disproved for the liver in man by Wood (1940). From our experience of the effects of venesection, about a litre of blood would have to be trapped out of the

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THE EFFECTS OF TRAUMA, DIRECT AND INDIRECT, ON THE HEART[1]

By HUGH BARBER

(From the Derbyshire Royal Infirmary)

CONTENTS

Introduction

Traumatic lesions of the heart may result from violence which is direct or indirect. In some events both may act together. For convenience of description the subject may be divided into cardiac disorders resulting from certain types of trauma—penetrating wounds, non-penetrating wounds or contusion, primary cardiac overstrain; and cardiac disorders which may occasionally be attributable to trauma—angina of effort and coronary thrombosis, disorders of rhythm, valvular lesions.

The older records have been concerned chiefly with wounds, rupture of the heart, or valvular lesions. The clinical evidence has been well defined and the morbid anatomy indisputable. In more recent years contusions, coronary artery disease, and arrhythmias after trauma have been studied more fully. The clinical aspects in many cases closely resemble those of disease due to natural causes. In these circumstances a judicious assessment of the history is essential, and a knowledge of such proof of trauma as has been obtained in similar events. There is at the present time a considerable number of records

[1] Received August 15, 1944.

which prove that the heart may be injured in many ways, with survival of the patient. The morbid anatomy is not available for study and can only be assumed by analogy. In some cases there are exceptional clinical symptoms or signs which suggest a traumatic lesion, in others there may be symptoms of cardiac origin which are of a kind quite unusual in the particular type of patient in question. After injury, however, we may meet with lesions or disorders of the cardiac mechanism which are indistinguishable from those produced by disease or by functional disorders which are not of cardiac origin. For these reasons the subject must be approached with an open mind.

There are occasions when the medico-legal aspects of the problem require consideration, but no attempt is made in the present paper to reach a finality which would satisfy the legal mind. Litigation is discussed only in so far as it may have a bearing on the symptoms and prognosis.

For the more recent observations and studies reliance is placed on the publications of Bright and Beck (1935), Warburg (1938), and White and Glendy (1941). The cases which have come under my own observation are summarized in Table II. Reference is made to the work of Külbs and Strauss (1932) and Schlomka (1934) in relation to induced trauma in animals, but the clinical evidence in the German and French literature is not reviewed fully, although reference is made to the evidence from these sources to be found in Warburg's (1938) monograph and Brahdy and Kahn's (1941) volume.

CARDIAC DISORDERS RESULTING FROM TRAUMA

Penetrating Wounds of the Heart

It is proposed to discuss only some general principles with regard to penetrating wounds of the heart from cutting instruments or projectiles. Occasionally a fractured rib may cause a penetrating wound. For clinical purposes, wounds may be divided into two varieties. Firstly, those in which there is a free communication with the pleural cavity or the outside; in this event, death usually supervenes quickly. Secondly, wounds which give rise to accumulation of blood in the pericardial sac, causing compression of the heart with the symptoms and signs of heart tamponade (see haemopericardium). Beck (1926) and Bigger and Porter (1934) have reported successful suture with recovery in this type of case. Bean (1941) reported a successful result of operation when the heart muscle was partially severed. Recently Blalock and Ravitch (1943) have suggested more conservative measures, and recommend that the blood should be aspirated once or twice, after which operation should be performed if bleeding recurs. Bullock (1936) reported successful suture of a wound in the right ventricle in a man of 20 years whose heart had ceased to beat before the operation had reached the pericardium. The patient was in good health nine years later. Bullock believes that the opportunity should be taken of attempting suture in hearts which have ceased to beat only for a few minutes, or perhaps up to a period of half an hour.

Foreign bodies inside the heart or in the heart wall present a difficult surgical problem. They may move, but there is evidence that in a number of cases a foreign body in the myocardium may become encysted in the ventricular wall, causing little inconvenience. Of this event Turner (1940) has recorded the case of an officer of 32 years who came under his care in 1917 with a machine-gun bullet in the wall of the left ventricle near the apex. The patient has led a normal active life with the bullet in the same position for 23 years. On the other hand, Burgess (1934) recorded the successful removal from the posterior aspect of the left ventricle of a machine-gun bullet which was causing trouble. It had entered six years previously, and in the last four years there had been attacks of pain, palpitation, and dizziness. At the time of record, 14 years after the operation, the man reported himself as perfectly well.

With a piece of projectile lodged in the myocardium, there may be evidence to suggest a contusion. Lea (1917) recorded complete heart-block in a soldier aged 20 years, in whom there was a piece of shrapnel lodged near the apex of the heart. He commented on the fact that the shrapnel was not near the bundle of His. From evidence furnished by more recent examples of heart-block the result of myocardial contusion in non-penetrating injuries, it seems probable that a contusion was the explanation. There was no opportunity to follow up the case. In the Derbyshire Royal Infirmary recently we had an example of myocardial bruising in a man 39 years of age, who was wounded by the discharge of a shot-gun. The charge entered the left pectoral muscle and the shot passed into the axilla, but none entered the thorax. An electrocardiogram showed a negative T-wave in Lead II, which became positive by seven days later. He recovered completely. These two cases indicate that an electrocardiogram may not help in locating a bullet.

Edwards (1943) stated that the number of casualties surviving gunshot wounds of the heart was small in the war of 1914–18, but there was no series published. He pointed out that the radiological technique of locating a foreign body in the heart is not easy. Holman (1944) described a case in which a machine-gun bullet was overlooked on the first radiological examination, but was discovered when the man was re-examined on account of chest pains, extrasystoles, and dyspnoea. He stated that non-intervention is correct when foreign bodies in the heart produce no symptoms. Sauerbruch (1942) is in agreement, but believes that symptoms tend to develop later. Sometimes, however, these are of a functional nature on account of the patient's knowledge of the condition. Turner (1941) has expressed the modern view of the subject in an article on gunshot wounds of the heart.

Non-Penetrating Injuries of the Heart and Pericardium

Aetiology and morbid anatomy. In considering traumatic lesions of the heart which are the result of direct violence we may assume in many cases that the heart was previously normal. It is true, however, that the diseased heart is more liable to injury, and this is particularly important when

considering lesions possibly associated with coronary artery disease. Furthermore, in assessing the significance of symptoms, any psychoneurotic tendency must be taken into account.

The type of accident. The accidents which have been proved to give rise to non-penetrating injuries of the heart have been most frequently crushing injuries of the thorax, blows over the front of the chest, or a fall from a height. So that there can be no doubt examples are taken chiefly from those accidents in which the heart was ruptured. The liability of children and young adults to accidents in general has furnished evidence from healthy tissues free from disease or degeneration. It is important to realize that there need be no fracture of bones of the thorax or any bruising. This is true for persons of any age, but more particularly in the young with elastic chest wall. Hamilton (1934) recorded rupture of the heart in a child, and Bilderbeck (1919) in a young adult, without any other evidence of trauma, and Barber and Osborn (1941) a large contusion of the left ventricle which caused death in five hours, and was the only lesion. There are many similar records, but of course fracture of the sternum or ribs may increase the liability to heart injury. Hawkes (1935) investigated the reports of more than 7,000 fatal accident cases. There were 70 examples of heart trauma, in 10 of which there was no fracture, and in seven of these no external mark of injury.

The evidence in general comes chiefly from the accidents of traffic and industry, with a few from sport. Of crushing injuries, we have examples of a man caught between two buffers, or knocked down and run over. The steering-wheel accident, in which the driver of a car bumps the front of his chest on to the wheel during a head-on collision, is fairly common. Blows over the front of the chest have come about from causes too varied to enumerate, but in some instances there has been serious heart injury from a blow that was not exceptionally severe. When the heart is ruptured as the result of a fall from a height (Howat 1920), it may not be possible to say how the trauma came about. Osborn's (1943) evidence concerning slight tears and contusions of the auricle suggests that these may arise on some occasions from force not obviously directed towards the heart.

Wilson (1943), in a study of blast lesions of the thorax, although chiefly concerned with the lungs, noted several examples of contusion of the myocardium, one rupture of the aorta, and many times small areas of haemorrhage in the anterior mediastinum. He was not able to decide which were the result of pure blast and in which contusion of the chest had arisen from direct injury. Beck (1935), analysing a large number of examples of traumatic rupture of the heart, believes that if the legs and abdomen are engulfed when a man is partially buried, the heart may rupture from indirect violence due to internal pressure. Saphir (1927) recorded rupture from indirect trauma in a boy four years of age who was run over, and Stephens (1922) made a similar suggestion in the case of a youth of 16 years whose abdomen was crushed, but both based the claim chiefly on the lack of

evidence of any thoracic injury, apart from the heart. After reading the histories, I should conclude in both cases that the heart was ruptured in the usual manner by compression of the elastic thorax. Swineford (1932) has recorded rupture of the heart from indirect trauma, but the patient was a woman 75 years of age who was struck from behind by an automobile; there were several fractured ribs and direct violence cannot be excluded. The practical significance of the study of accidents which have led to fatal heart lesions is in connexion with the clinical possibilities of less serious conditions which may arise. The heart should be examined after a crushing injury of the thorax, a blow over the front of the chest, or a fall from a height, whether or not there is evidence of bruising or fractures.

The post-mortem evidence. Bright and Beck (1935) and Beck (1935) analysed 152 cases of traumatic rupture of the heart. They found that any one of the four chambers of the heart might be ruptured, and no one chamber more commonly than the others. Warburg (1938) stated that injury of the left ventricle is less likely to have a fatal termination. It seems that 76 of Bright and Beck's series died of heart tamponade from haemopericardium. The interventricular septum was ruptured in 11 cases. They also analysed 11 cases in which death was due to myocardial failure without rupture, and recorded various myocardial bruises. They proved that trauma which appeared to be directed to the front of the chest might give rise to a lesion on the posterior aspect of the heart. They also gave an account of 12 recorded cases of myocardial contusion with recovery. The diagnosis was made on the clinical evidence. They pointed out that these figures (in 1935), which give such a high proportion of recorded fatal cases, are an indication that the clinical condition of myocardial contusion is frequently overlooked. Osborn (1943) in the Derbyshire Royal Infirmary and in the coroner's mortuary carried out 262 autopsies on fatal accident cases. In 19 there was evidence of heart trauma. There were serious multiple injuries in many, and most of the heart lesions were such as would be compatible with survival and complete recovery. Both the front and back of the heart showed bruising from direct violence. He drew particular attention to a lesion of the pericardiophrenic angle, where he found bruising on the posterior aspect of the right auricle near the entrance of the inferior vena cava, tending to spread upwards. This is of considerable significance in relation to disorders of rhythm. He noted that it is likely to be overlooked unless specifically sought. It was the commonest heart lesion in his series, but the figures are incomplete, because in the earlier records it may have been overlooked.

Glendy and White (1936) stated that 'in 7,600 autopsies at the Massachusetts General Hospital, where there is a busy accident service, it happens that there is not a single case of cardiac trauma of any type on record'. It is possible that similar records would come from many pathological departments. Heart trauma is a rare cause of death, but minor degrees of myocardial bruising are fairly common in those who have died from some other cause after a serious accident. Warburg (1938), in an analysis of 60 cases

which came to autopsy, noted fibrinous pericarditis in seven, adherent pericardium in one, and mentions the so-called 'milk spots' and scars. No doubt this kind of lesion is met with in those who survive for a reasonable time. Bright and Beck (1935) found pericardial adhesions two or three months after they had bruised the hearts of dogs. Kissane (1937) described two fatal cases with some myocardial bruising, but the chief abnormality was haemorrhage into the mediastinum at the base of the heart. A similar finding was met with at the Derbyshire Royal Infirmary. Leinoff (1940) stated that the post-mortem reports on 50 non-selected fatal automobile accidents revealed eight examples of heart trauma. There was one with rupture of all four chambers, one with a tear of the tricuspid valve, one with acute dilatation of the left ventricle, and five with subendocardial haemorrhages and haematomas of the heart muscle and pericardium.

Contusions described in the myocardium of the right or left ventricle have varied in size, and in some cases have been multiple. When death has not resulted from rupture of the heart, the bruise has usually been spreading chiefly from the pericardial surface inwards, as in two examples from this hospital (Barber, 1940; Barber and Osborn, 1941). When the heart has ruptured after a delay of some days, there is evidence to suggest that the original lesion was in the endocardium. We have had one specimen in this hospital in which the only lesion in the left ventricle was a tear from the endocardium which penetrated one-third of the way through the heart wall. There were multiple injuries of the brain and other organs, which would account for the fatal termination. Hume (1941) described a similar finding in a man who died from multiple chest injuries and a ruptured liver. In the left ventricle there was a laceration two and a half inches long extending from the endocardium to a thin layer of muscle in the epicardium. This question of a contusion beginning in the endocardium will be discussed under the headings of delayed rupture of the heart and of cardiac aneurysm. Of healed scars in the endocardium, I know of no recorded evidence.

Animal experiments. The German records are taken from Brahdy and Kann (1941). This work was begun by Külbs in 1909, and Külbs and Straus (1932) recorded injury of the heart in dogs with the skin and thorax intact. They noted bradycardia in some cases. Schlomka (1934) produced haemorrhages in the myocardium, and noted a fall of arterial blood-pressure and rise of venous pressure. Acute dilatation of the heart was common. Temporary abnormalities were present in the electrocardiographic tracings, which he thought might be due to spasm of the coronary arteries. Some disorders of rhythm were recorded. Bright and Beck (1935) bruised the hearts of 25 dogs. One died shortly after from myocardial failure, and two of ventricular fibrillation. The hearts had been exposed under anaesthesia before the trauma was applied, and the actual bruising was observed. It was surprising to find what extensive bruising was compatible with recovery. They noted cardiac dilatation. Usually there was tachycardia, but occasionally bradycardia. There were abnormal electrocardiograms indicating myo-

cardial lesions. Haemorrhage into the interventricular septum was met with. When the dogs were killed two or three months afterwards the myocardial damage was repaired and there were pericardial adhesions. Kissane, Fidler, and Koons (1937) carried out experiments on dogs which produced similar results, although they noted also one valve ruptured and sometimes haemorrhage into the base of a valve cusp. One of their animals died of ventricular fibrillation. Moritz and Atkins (1938) after experimental work on animals compared the scars resulting from contusions with those after infarction due to natural causes, and could find no distinctive features. Zuckerman, Krohn, and Whitteridge (1942) carried out experiments on animals with reference to the results of blast. Although primarily interested in the lungs, they found some myocardial injuries and some abnormal electrocardiograms. It is unnecessary to give details of the electrocardiograms met with in experimental work, because they are very similar to those found in clinical examples of myocardial contusions and will be described there.

Routine electrocardiography after trauma. From this hospital (Barber, 1942) were published the records from 33 accident cases, and the series is now extended to 75. Electrocardiography has been a routine in patients who came to the casualty department, or were admitted to a surgical ward, on account of some thoracic injury. None are included unless seen within 48 hours of the accident. The cases were unselected, being examined as opportunity arose. The symptoms will be discussed in relation to the clinical features of myocardial contusion. There was, of course, a full physical examination in addition to a routine electrocardiogram using the four standard limb leads. Among the 75 patients there were 20 with an abnormal electrocardiogram. In two cases it was not possible to repeat the examination, because serious lung contusions led to a fatal termination from pneumonia. One of these cases, with paroxysmal tachycardia, showed a little bruising of the right auricle. In the other there was no post-mortem evidence of myocardial bruising, 12 days after the T waves in Leads I and II had been flat or slightly inverted. In one patient partial heart-block persisted permanently. In the other 17 the electrocardiograms all returned to normal in a comparatively short time. This is accepted as evidence that the abnormalities were the result of trauma. These temporary abnormalities were found most frequently one or two days after the injury. On several occasions there was a normal tracing a few hours after the accident, whereas 24 or 48 hours later abnormalities appeared. This was followed by a normal tracing, sometimes a few days subsequently, and in other cases in the second or third week. In at least two patients it was possible to demonstrate radiologically a small amount of fluid in the pericardium at a time when the electrocardiogram had returned to normal. In one or two elderly men it was four or five weeks before an abnormal T wave in Lead I became upright. The abnormalities are set out in Table I. Premature contractions were met with, but not frequently, and no attempt is made to assess their

significance. The T wave in Lead III was inverted temporarily on one or two occasions, but it seemed possible that this was the result of a change in the height of the diaphragm. None of the patients had a pneumothorax, which is important, because Master (1927) showed that this condition may change the electrocardiogram temporarily. All the tracings were taken with the patient lying down, which is noted because White, Chamberlain, and Graybiel (1941) have shown that, very exceptionally, the T waves may vary with the position of the patient. The trauma itself was of such varying type and degree that a much larger series would be required for an analysis into age groups, or the liability of particular accidents to cause heart lesions. But there is confirmation of the experimental work in animals, and there are certain deductions which can be referred to when discussing clinical cases. The series seems to confirm the belief that an electrocardiogram should be taken soon after the accident and repeated subsequently. An electrocardiogram is a guide in both diagnosis and treatment, but the comparatively high proportion of temporarily abnormal tracings in the present series should not be accepted as evidence that heart disease of clinical significance is so common after trauma.

TABLE I. *Routine Electrocardiogram within 48 Hours of Trauma*

P waves inverted	1	T waves of exaggerated amplitude	2
Supraventricular tachycardia	2	T 1 flat or inverted	5
Sinus bradycardia	3	T 1 and 4 flat or inverted	1
Partial heart-block	1	T 1 and 2 ditto	2
R waves slurred	1	T 2 ditto	1
		T 1, 2, and 4 ditto	1
Total number of patients	75	Number of abnormal tracings	20

The records of 33, with eight abnormal, were published (Barber, 1942).

The Pericardium

A pericardial friction sound as evidence of heart trauma has been recognized for a long time in surgical accident wards, but it is not met with frequently. The time of its appearance is variable and the sign is evanescent. The case of contusion of the heart reported by Smith and McKeown (1939) is a good illustration. A youth 17 years of age received a blow over the chest in a motor accident. He sustained head injuries, but was getting about on the seventh day when pain developed in the chest. A pericardial rub was detected only on the following day, after which it disappeared, and did not recur. On the eleventh day the electrocardiogram gave a tracing suggesting pericarditis, of which a series of changing pictures were recorded over a period of two months. He had recovered in six months' time. It is probable that bruising of the parietal and visceral layers of the pericardium may exist without there being any physical sign in the way of friction, which will depend upon the state of the serous membranes and may develop as the bruising becomes more organized. There may be some dyspnoea, but pain is not constant, although the symptoms which result

from the associated injuries may obscure the picture. Evidence of pericarditis is an indication for a full cardiological investigation. If there is no underlying heart lesion, complete recovery is to be expected. Occasionally one reads of a 'to and fro' bruit at the base of the heart, which has disappeared. Although the writer may have connected this with a possible lesion of the aortic valves, it is more probable that the sign was the result of pericardial friction. Temporary dilatation of the aortic ring after injury has not been described. Williams (1936) reported temporary aortic regurgitation, which he attributed to oedema of the valve cusps, in a youth aged 18 years who sustained a contusion. There was immediate tachycardia. Next day aortic incompetence was diagnosed, but soon afterwards a pericardial rub was recognized. An electrocardiogram showed abnormal T waves. By the fifth day the signs had cleared. It is possible the abnormal sounds were pericardial in origin.

Pneumopericardium. Warburg (1938, 1940) analysed the records of 225 cases of heart trauma which he considered well substantiated. There were 10 examples of pneumopericardium in which the cardiac dullness disappeared and there was a splashing sound, or *bruit de moulin.* In the six case histories which he grouped together there was only one fatality. It is of interest that these six were recorded between the years 1844 and 1880. Three cases, the result of war injuries, have been recorded recently by Kern and Godfrey (1943). Nixon (1941) pointed out that physical signs in thoracic injury may be difficult to interpret, and wrote 'never diagnose haemopneumopericardium until you have seen the pericardium exposed either during life or after death'.

Purulent pericarditis. Warburg's (1938) series contained four cases of pericarditis with pyogenic infection, all of which ended fatally.

Haemopericardium. This is the most important pericardial condition for consideration in connexion with non-penetrating wounds of the heart. Small amounts of haemorrhage may account for some of the symptoms in a case of myocardial contusion. With a large haemopericardium, the symptoms and signs of heart tamponade develop. There is shock, the blood-pressure is low, and perhaps the pulse-pressure as well. There is a tendency to bradycardia. The veins in the neck are full, the skin is cold and dusky, with a tendency to sweating, and the heart sounds are distant. Radiology will confirm the diagnosis. Wood (1937) has described a characteristic electrocardiogram, in which the tracing resembles that of coronary thrombosis, but with the changes most pronounced in Lead II.

Moullin (1897) gave the record of a man 20 years of age who was struck over the sternum by an elbow whilst playing football. He continued to play, but collapsed 20 minutes later. More urgent symptoms developed 36 hours subsequently, but it was not until the twenty-fifth day that Moullin incised the pericardium and let out a considerable quantity of thin blood-stained fluid. The patient recovered completely and was playing football again within less than a year. Rajasingham (1939) described a

haemopericardium, confirmed radiologically, in a young woman after a blow. Six ounces of blood were aspirated and she made a complete recovery. We have had one example in this hospital, in which the effusion was absorbed naturally without aspiration, but the symptoms and signs were characteristic. The two proved cases which are cited above are important from the point of view of treatment. As already stated, Bright and Beck (1935) found records of 76 cases of heart rupture with death from heart tamponade. They held the view that many of the cases are amenable to cure by operation and suture. There is a record by Turner and Gould (1917) of a small tear in the right ventricle, which would seem to be a case in point, but the indications for operation are more obscure than when heart tamponade results from a penetrating stab-wound.

The Myocardium

Rupture of the myocardium may be either immediate or delayed. Immediate rupture has been considered in the morbid anatomy section, and with haemopericardium. There is little likelihood of spontaneous rupture of the heart being confused with a traumatic lesion. The post-mortem findings will be characteristic. Goodall and Weir (1927) recorded 18 cases, but in only four was there evidence of emotion or strain. Such an event would not be included in trauma of the heart in medical case histories. Nice points of law are not within the province of the medical man. A few years ago a man in this district died of spontaneous rupture of the heart whilst sitting in a doctor's waiting room, just after the news had come through on the wireless that England had been defeated in a cricket match in Australia.

Delayed rupture of the heart is a rare event, but one of considerable interest. Groom (1897) was called to a boy of 16 years of age who had collapsed while walking, and found him dead. A month previously the shaft of a pony trap had pressed him against some railings. He was in bed for five days. There was no external bruising. *Post mortem* the left ventricle was seen to be ruptured posteriorly. The lesion appeared to have developed from the endocardium outwards, with eventual haemorrhage into the pericardium. This case history illustrates the essential features of 12 examples of delayed rupture of which I have read the notes. Eight of the patients were children or young adults with elastic thoracic walls. Most of them sustained a crushing injury, although not apparently severe. Priest's (1939) case was that of a young sepoy struck over the front of the chest by a cricket ball whilst wicket-keeping. After a short rest he continued to play, as he did also the next day, but died suddenly on the evening of the second day from a rupture of the right ventricle. His history is a good illustration of the symptomless nature of the lesion, which is common to all 12 cases, none of which had been under observation for any symptoms connected with the heart, and some of which had not had any medical attention. Tuohy and Boman (1931) reported the case of a man 63 years

of age who was injured by a steering-wheel accident and continued with his duties although feeling weak. He died suddenly whilst laughing two weeks after the accident. There was some disease of the coronary arteries and rupture of the left ventricle.

The post-mortem records are mostly incomplete, but French (1912) recorded rupture of an aneurysm from the upper part of the left ventricle in a child three years of age who had fallen from an upstairs window. This rupture took place on the twenty-first day, when there had been no suspicion of a heart lesion, although the child was in hospital all the time and an operation had been performed for a fractured femur. Hawkes (1935) described rupture of a traumatic aneurysm of the left ventricle in a boy six years of age three months after an accident. He had been one week in hospital, but had then resumed a normal life and died quite suddenly. These two patients with aneurysmal dilatations which ruptured seem to confirm Groom's (1897) note that the heart had ruptured from the endocardium outwards. We have one specimen in this hospital from the accident post-mortem table in which there is a tear of the endocardium and a partial rupture of the left ventricular wall. The patient had died of multiple cranial and other injuries. This endocardial lesion alone might have been symptomless until rupture took place. Glendy and White (1936) have recorded an interesting heart lesion of this kind. A man 24 years of age was involved in a serious motor accident. The heart was passed as normal and a ruptured spleen was excised. He died from shock, loss of blood, and lung complications. At autopsy the anterior papillary muscle in the left ventricle was ruptured at the base, and the tear extended one cm. into the myocardium; there was a purplish spot on the external surface of the ventricle.

Delayed rupture of the heart is, of course, a rare event. It is tempting to believe that the essential lesion is probably a tear in the endocardium. Some of the patients, if more carefully examined, might have given evidence of suggestive symptoms or signs, but it is reasonable to suppose that a tear in the endocardium would be less likely to give rise to symptoms than would a contusion or partial rupture which involved the outer surface of the heart and the pericardium. Krumbhaar and Crowell (1925), for example, reported fatal rupture of a traumatic infarct beginning in the outer part of the left ventricle in a man 38 years of age. For several days he had suffered from severe praecordial pain, although no diagnosis was made during life. Bright and Beck (1935) suggest that the second week is the critical period, during which rupture is most probable. In the particular group of 12 clinical histories under discussion, three patients died in the first week, three in the second, and six survived for a period varying between 21 days and three months. After an accident in which there has been a crushing injury of the chest, it would be good practice to observe the heart over a period of several weeks. This need not foster the development of a neurosis, which is most liable to arise in circumstances in which the normal heart has received by mistake a label of disease. There are no records by which to

decide whether an electrocardiogram would show evidence of a lesion beginning in the endocardium.

Contusion of the myocardium. The aetiology and morbid anatomy have already been discussed. White (1937) stated that contusion is probably fairly common and recovery the rule. From the evidence obtained with the electrocardiograph and from autopsies of accident cases, where small lesions compatible with recovery are common, it seems probable that symptomless cases with recovery are by no means rare. On the other hand, patients in the accident wards with fractures of bones of the thorax or with contusions of the lung, haemothorax, or pneumothorax, will have symptoms which may mask those which might arise from a contusion in the heart-muscle. Furthermore, the rest in bed necessitated by some surgical lesion may tend to keep in check symptoms referable to the heart. For these reasons the more striking clinical histories may sometimes be obtained from the family doctor of a patient who does not come for full investigation until a time when the evidence from physical signs is tending to pass off. One example of this (Barber, 1940), in a healthy man 40 years of age who was struck over the front of the chest by a block of limestone, furnished a history that may be divided into (1) the accident, (2) an interval, (3) an urgent attack of dyspnoea, (4) gradual recovery with rest in bed, and (5) complete recovery. This has been maintained for six years. There was no proof, because a full investigation took place only a month after the accident. A recent case reported by Lee, Ussher, and Houck (1943) gives such a similar story, with proof from physical signs, that it may be cited as characteristic of an uncomplicated case of myocardial contusion. The patient was an aviation cadet aged 22 years. The accident was a blow over the lower sternum from an elbow while playing football. The immediate symptoms were that he was stunned and thrown to the ground, but was playing again within a few seconds. The interval before serious symptoms developed was 12 hours, when there was pain over the lower part of the sternum, dyspnoea with orthopnoea, and constricting chest pain radiating to the jaw. The findings were negative, although a slight abnormality was suspected in the electrocardiogram, and possibly a little blood in the pericardium. He was discharged from hospital seven days after the accident, but re-admitted two days later with urgent dyspnoea and rapid heart action. There was deep inversion of the T-wave in Leads I and IV, most pronounced 15 days after the accident. The dyspnoea and pain were controlled only by rest, but eventually he made a complete recovery.

Particular stress should be laid upon the interval between the immediate reaction to the accident and the appearance of symptoms referable to the heart. In both these cases it was about 12 hours. Beck (1935) described the case of a man who died on the sixth day. His urgent symptoms developed on the third day, there was electrocardiographic confirmation, and a contusion was found *post mortem*. Warburg (1938), in discussing this interval in 51 indubitable cases of non-penetrating injury of the heart which came to

autopsy, stated that in 15 there were no symptoms suggesting a heart lesion immediately after the accident. It appears that many of the accidents were serious with associated injuries, making it difficult to analyse the symptoms. In uncomplicated contusions a latent period seems to be the rule rather than the exception.

When symptoms develop, there may be a little frothy expectoration. There is dyspnoea with orthopnoea, there may be a feeling of faintness, there is praecordial pain or discomfort, and the blood-pressure is low. The pulse-rate is variable, but tends to be accelerated. Of physical signs Bright and Beck (1935) think the heart sounds are characteristically short and faint, but the electrocardiogram is more important. Tracings which resemble those of coronary thrombosis are the most convincing, but flat or inverted T waves, T waves of exaggerated amplitude, large Q waves, and slurring or notching of the QRS complex have been met with. In a favourable case improvement in the symptoms gradually sets in, but relapse may occur if the period of rest is insufficient. On two occasions in this hospital we have met with frothy expectoration and physical signs indicative of pulmonary oedema. One case which ended fatally has been mentioned in the morbid anatomy section of the present paper (Barber and Osborn, 1941) and the other made a complete recovery. It seems reasonable that when symptoms suggesting contusion are present, or certainly if the electrocardiogram is abnormal, not less than a month in bed is required. From our experience and the recorded examples in the literature, it is possible to deduce that neglect of symptoms may delay, or possibly prevent, complete recovery.

Complications of myocardial contusion. Haemopericardium has been discussed. Acute dilatation which has been common in animal experiments has not, according to White and Glendy (1941), been observed in clinical medicine except in hearts already diseased. There is a recent record (Froment, Camelin, and Blanchard, 1941) which suggests this probability in a soldier 26 years of age who was struck over the front of the chest by the recoil of a gun. He fainted but was on duty next day. Ten days later there was haemoptysis, which recurred, and radiology revealed a large heart, which was obvious clinically three months after the accident and was confirmed at autopsy six months after the injury; there were signs of myocardial trauma.

A valve may be ruptured by direct violence, and this accident will be considered in another section. The valve lesion is usually the predominant feature, but Anderson (1940) described an interesting case in which there was definite evidence of myocardial injury, proved by an electrocardiogram, simulating the picture of coronary thrombosis, and in addition a systolic bruit and thrill suggesting a lesion of the mitral valve or rupture of the interventricular septum. The accident arose when a steeplechase rider, 30 years of age, was thrown at a hurdle and stepped on by a following horse. A year later he was taking all ordinary exercise without discomfort, although the abnormal physical signs were still in evidence to some extent. It is this

recovery of function which makes it difficult to assess the question of a valve lesion. Cameron (1942) has described a somewhat similar clinical history in a builder's labourer aged 35 years who fell from a scaffold, fracturing his left clavicle. Ten days later he was taken seriously ill with fainting, tachycardia, and congestive failure. A loud systolic bruit developed in the mitral area. Three years later he was reported to have recovered, the systolic bruit being audible but less intense. It does not seem possible to suggest a definite diagnosis, but probably the heart was injured as the result of contusion.

Arrhythmia after trauma will be considered in another section. There are cases, however, in which it is obvious that the disorder is associated with a bruise of the heart muscle and, of course, heart-block is due to bruising of a particular area of the myocardium and for convenience is considered with other disorders of rhythm.

Sequels of myocardial contusion. Cardiac aneurysm is a rare but recognized sequel. Warburg (1938) quotes (Hildebrandt, 1898) the case of a boy nine years of age who fell downstairs and did not recover fully. When he died aged 27 years an aneurysm of the left ventricle was found at autopsy. Joachim and Mays (1926) recorded the case of a boy of 12 years who was run over. He had a few attacks of tachycardia in the years following, and when he died 13 years after the accident there was a large aneurysm of the left ventricle near the apex. O'Farrell (1939) described aneurysmal dilatation commencing in the lower part of the left ventricle in a man who had developed auricular fibrillation after a steering-wheel accident, and died three months later of heart failure.

Angina of effort may develop in convalescence from a proved myocardial contusion, if the period of rest has not been adequate. It may persist for a few months with complete recovery subsequently, in which event the relation to injury is reasonably convincing. The problem of angina after trauma merits discussion in a separate section.

Persistent functional incapacity of the heart is a difficult problem. White and Glendy (1941) draw a distinction between a true cardiac neurosis, in which a man believes his heart to be diseased, and the condition of neurocirculatory asthenia, in which the incapacitating symptoms are present, but not the fear of heart disease. I have the records of several men, one of which is published (Barber, 1938), who have been short of breath and dizzy, especially on stooping, after a severe chest injury. The condition has resembled the myocardial weakness of the senile heart in that there was no discomfort at rest or on moderate exertion, but a consistent inability to respond to anything like the pre-accident capacity. There has not been the variability, the sweating, or the nervousness of the obviously neurasthenic patient. Platt (1940) and others have described similar cases. A full investigation, including radiology of the lungs is, of course, indicated. There may be no genuine heart disability at all. The cases are not numerous, but they would merit special consideration in a rehabilitation scheme, and when there is a doctor attached to some industrial organization where the accident took place, it

would be wise for him to be in touch with the patient early in convalescence after the injury. Beck (1935) described the case of a doctor whose heart showed no abnormalities, but in whom symptoms of distress on exertion had persisted for 17 years after a motor-cycle accident. His symptoms when an attack was deliberately courted for observation were quite alarming, which may have been due to suggestion, but it seems probable that his disability was myocardial weakness which had resulted from a serious chest injury. The athletic man is not immune from the possibilities of suggestion, but it is of interest that in the archives of journalism there is the record that a distinguished amateur fast bowler never again sent down the same lightning deliveries after being struck over the front of the chest by a cricket ball whilst batting.

I have a recent example in a soldier aged 30 years who two years ago was in hospital seven weeks with chest injuries after a motor-cycle accident. He was three months off duty and then was all right with gentle exercise, but had pain and shortness of breath if he exerted himself. When I examined him the heart was quiet and steady. He was not surprised to hear that a full investigation revealed nothing abnormal. It is an unconfirmed case history, but not quite like a cardiac neurosis, the effort syndrome, or neuro-circulatory asthenia.

Primary Cardiac Overstrain

It would be outside the scope of traumatic lesions of the heart to discuss over-stress in athletic events. The trained athlete has no liability to such disorders, nor has the untrained unless perhaps in rowing or some climbing adventure in which at times the chest is fixed with the glottis closed. A disability in these circumstances must be very exceptional, although the presence of some more or less latent infection may be a predisposing cause. The intense effort with the chest fixed and the glottis closed, an effort which is unexpectedly prolonged, is in a different category, and merits consideration although a true disability after such an effort is a clinical rarity. The effort in question is usually one of lifting a heavy weight, with perhaps a history of slipping or being in some unusually cramped position. There may have been exceptional strain on the pectoral muscles in some cases. We may get a history of a similar event unrelated to industry or any compensation liability. The sequence of symptoms immediately after the effort is faintness, dizziness, discomfort in the chest, palpitations, and shortness of breath. A complete physical examination rarely takes place until at least a few days after the event. There may be some premature contractions and a cardiac impulse unduly palpable from forcible beating, but radiology reveals a heart of normal size. Although it is not possible to demonstrate any structural change in the heart, an intense effort with the chest fixed and the glottis closed does sometimes appear to have disturbed the functional capacity of the heart for a varying period of time. It may be a true cardiac neurosis which has developed because an erroneous diagnosis of a dilated heart has

been made after a medical examination. Such a neurosis may also result from the false interpretation of pain over the front of the chest. Such pain is very unlikely to be cardiac in a case of this type, but may be due to rupture of pectoral muscle fibres or some similar lesion. During the time of the effort there may have been fear or anxiety which will predispose toward a neurosis. Later, impending litigation may be detrimental. There remain, however, a few cases in which none of these possibilities arise. The response of the heart to exertion is poor, and the history of the symptoms is clear and unequivocal. Although there are no physical signs to confirm the diagnosis, it does seem probable that over-stress of the heart has resulted in strain.

Kahn and Kahn (1927) analysed 20 cases of heart strain, and admitted that the subjective complaints of the patients were the outstanding features. They included some older men, whose hearts were probably diseased. Of the six cases cited in the article there is only one, in a man aged 26 years, that I should regard as a case of primary cardiac overstrain. These authors seem to interpret pain in the chest as related to the heart, which I think is very doubtful. In treatment they do not appear to stress the fact that the patient should be assured that no evidence of structural abnormality can be detected, and they seem to advise too long a rest. It is a rare event, but I have two or three records which have seemed convincing. In one (Barber, 1938) in which there was no claim for compensation, an athlete aged 30 years in good health suffered from disturbed function of his heart for a long period as the result of an arduous lifting and carrying effort, during which he had slipped, thereby intensifying the strain. Price (1937) defined primary cardiac overstrain as a cardiac disorder which is the immediate result of excessive or injudicious physical exertion in a person whose heart was previously normal. Allbutt (1909), who first wrote on the subject of heart strain in 1870, believed that over-stress of effort might end in strain, but he taught that for one disability due to strain there are 50 of secondary or incidental derangement. This teaching is a good corrective to the erroneous diagnosis of heart strain which at one time was commonly made on no better evidence than lassitude after some prolonged exertion and the physical finding of a bruit. But Allbutt on clinical evidence believed that heart strain with subsequent ill effects, usually temporary but occasionally more or less permanent, might occur as the result of exceptional effort. In the management of a case of alleged heart strain, physical examination should be directed toward the demonstration that no evidence of structural disease is manifest. Pain, if present, must be accounted for by some lesion unconnected with the heart. It should be possible to give a favourable prognosis, avoiding the anxieties of litigation over the question of any cardiac disability. A cardiac neurosis may result from the heart's being mistakenly given a label of disease after some physical examination. The effort syndrome is often attributable to emotional causes. There is no proof that a normal heart can suffer as the result of strain, and to base a diagnosis on the probabilities of the history and the symptoms is unsatisfactory. Nevertheless, if we have the

right conception of the management of a possible case of primary cardiac overstrain, it may be wise to admit the possibility of its occurrence.

CARDIAC DISORDERS OCCASIONALLY ATTRIBUTABLE TO TRAUMA

Angina of Effort and Coronary Thrombosis

It seems probable that both angina of effort and coronary thrombosis may arise as the direct result of trauma, but the clinical features will be indistinguishable from those due to disease from natural causes. In these circumstances it is important that the clinical history should be taken carefully, without leading questions, and with a mind unbiased. This is equally true for patients with compensation liability and for those without, but in the former it is well to remember that the first history obtained is the most reliable. In most instances one may presume that the coronary arteries were already diseased, although there may have been no symptoms previously. The records are chiefly of older men, as one would expect, although disease of the coronary arteries may occur quite early in life, of which we are reminded by French and Dock (1944) who have published 80 cases of sudden death the result of coronary artery disease in soldiers between 20 and 36 years of age, of whom 90 per cent. were overweight. They state in the summary that in half of these men vigorous effort brought on the fatal attack, or that it occurred within a few hours after exertion. It seems, however, that marching with pack and other normal activities of soldiers were accepted as 'vigorous effort', so that the exertion in question was not exceptional, but merely the routine for young men. The patients died of coronary occlusion confirmed at autopsy. I think it is contrary to the experience of most of us that this event should be related to exceptional exertion. Sudden fatal seizures are outside the scope of trauma of the heart, but the evidence has some bearing on the question of angina of effort, and is particularly important with reference to coronary thrombosis after strain. Hume (1941) analysed 133 autopsies performed or seen by himself on coal miners who died suddenly in or near the pit. In all cases there was coronary atheroma. In 75 there was recent thrombosis, but in 58 no naked-eye evidence of this. In 29 there were no witnesses of the event. In the remaining 104 there was a clear account of the activities before death, and there were no histories of strain or injury. Only five were exerting themselves to an extent beyond ordinary walking and many were sitting still. The experience extended over a period of 30 years. He summarized his observations by saying that all had gross coronary artery disease 'with potential liability to a thrombosis at any moment'.

It is of the utmost importance to remember this evidence when considering clinical histories. Master, Dack, and Jaffe (1937) analysed the histories of 555 patients with coronary thrombosis. There were more than 800 seizures. They could find no specific factors which precipitated the attacks, which occurred 'irrespective of rest, activity, excitement, or emotion'. In two per

cent. there was strenuous exertion, in 5 per cent. excitement, and in one case there had been a blow over the front of the chest. Conflicting evidence is furnished by Fitzhugh and Hamilton (1933) who were studying the question of angina from the point of view of prescribing a suitable regime which would prevent the occurrence of a fatal attack. In 100 private patients they concluded that either a fatal anginal attack or coronary occlusion had been precipitated by unusual physical exertion on 56 occasions. They believed that the fatality could have been prevented. They were not concerned with the problem of accident, but were looking for evidence that by a careful regime such disaster could be avoided, and some of the evidence was from relatives who may have been wise after the event in finding some history of strain.

There is no doubt that in recent years a considerable amount of reliable evidence has been accumulating which proves that the heart may be injured by contusion. It is probable that a diseased heart-muscle or rigid coronary arteries would be disposed toward injury, but the clinical histories of coronary thrombosis after trauma do not furnish any additional evidence by way of proof, because of the known uncertainty of the natural history of the condition. Two important communications on contusion of the myocardium report the same story of a man who developed coronary thrombosis two days after being struck on the front of the chest by a golf ball. The original history comes from a column of 'Queries and Minor Notes' (1933) in which the case history is unsigned and the writer asks that his name should be withheld. It is a believable story, but cannot be accepted as a scientific record, or as any addition to the proof that direct violence may injure the heart. Although the significance of these general considerations is chiefly opposed to the view that a precipitating cause is of importance, one may meet with exceptional individual case histories, which seem to indicate that trauma or excessive strain may be a factor in bringing about the symptoms which produce disability.

Blackall (1813) described five cases of angina pectoris, of the last of which he wrote: 'The following as an instance not common, of the disease being connected with external violence, will perhaps be deemed worthy of the attention of the reader. R. B. aetat. 60, a coachman. Three months before he consulted me received a violent blow from the pole of a carriage, which forcing him against a wall produced some little contusion of the surface of the chest, and an internal pain, for which he was blooded, and used a liniment. He continued affected in his breathing on motion, and two months afterwards, whilst he was pitching some hay into a loft, he felt a violent pain in the region of the heart, spreading rapidly to the left arm, with faintness and inability of movement. A similar paroxysm came on several successive nights, waking him with an approach to deliquium and great anxiety. It continued to return on every exertion, and went off only by rest. But after he had quitted his situation, and was liable to less fatigue, the attacks became milder.' The record adds that after steadily improving he returned to his employment three years later.

Modern traffic and mechanized industry have increased the liability to accident of all sections of the community, which may be the reason why the relation of angina to injury has received little consideration until comparatively recent years. One example which seems convincing (Barber, 1938) was of a man aged 54 years who fell heavily on his chest. His doctor noted some irregularity of the heart. The angina of effort came on suddenly 14 days later when he first left his house on the way to work. It recurred over a period of two or three months, but gradually subsided. For six years he has remained perfectly well, and has played cricket in a village team. White and Glendy (1941) pointed out that nervous influences may play some part, but this did not arise in my patient, who had no compensation claim, no anxieties about his pay, and returned to his clerical duties before he was fit for his usual active recreations. Some variety of chest pain may remain after bruising, but in this man there was no such pain until the typical anginal attacks came on. He had remained at home on account of a sprained ankle. Campbell (1939) described this sequence in a man aged 47 years who was struck above the left nipple by a piece of furniture which pinned him against a wall. Severe angina developed two hours later as he was walking home. He was a man with arteriosclerosis and a raised blood-pressure. Seven years later he was still liable to the attacks. I have also seen two similar persistent cases in which the radial arteries were thickened and the blood-pressure raised. Warburg (1940) in his second series of traumatic heart lesions, which numbered 59, recorded 16 cases of angina.

That coronary thrombosis should develop after direct violence to the thorax seems a reasonable possibility when we review the morbid anatomy of myocardial bruising. Wearn (1935) described this event in a man 55 years of age who was struck over the chest by a piece of furniture. He collapsed but soon recovered, and a few days later there was a typical attack of coronary thrombosis. Starling (1940) saw a patient 60 years of age with coronary thrombosis 16 days after he had fallen down a hatchway and bruised his chest. He had carried on with light work in spite of pain until the serious symptoms developed. Leinoff (1940) described the case of a man 38 years of age who was struck over the front of the chest by a wave whilst bathing, and was thrown over. Coronary thrombosis developed the next day. Kissane (1937), Warburg (1938), and Sigler (1942) have recorded the event and Beck (1935) discusses the problem, citing examples. The interval between the injury and the typical seizure has usually been a few days.

It is unlikely that there would be much doubt about the accident in question, when direct violence is being considered. Coronary thrombosis after an excessive strain is a more difficult and doubtful problem. I have one case history (taken in association with P. H. O'Donovan) of a man aged 58 years who collapsed a few minutes after a very severe strain of pulling a cable. There is a history of symptoms suggesting coronary thrombosis, for which he was kept in bed for three weeks. Three months later an electrocardiogram confirmed the diagnosis. As a rare event, it seems a reasonable possibility

that the exceptional effort precipitated the attack. Boas (1939) claimed to have seen 25 patients in whom coronary occlusion appears to have been directly induced by severe or unusual exertion. The thrombosis was during or very soon after the effort, but sometimes there were only slight symptoms for a time. He suggested that the strain may rupture diseased capillaries or an atheromatous plaque. Paterson (1938) has supported this suggestion. Of the 14 case histories which Boas (1939) cites only five were entitled to claim compensation. His experience, as that of Fitzhugh and Hamilton (1933), appears to be exceptional. It raises the whole question of case-history taking. I have seen a patient recently with angina of effort, whose first thought was that he must have strained himself whilst gardening for such a pain to develop, although he knew of no specific event. His family doctor recognized the condition as angina, failing which in good faith a history of strain might have been recounted on the patient's visit to myself.

In those circumstances in which angina of effort comes on for the first time after a well-defined injury, and more particularly if the patient makes a good recovery, it is reasonable to connect the trauma with the clinical symptoms. If one studies the morbid anatomy of myocardial contusion met with in perfectly healthy hearts, it is clear that such bruising near a diseased coronary artery might lead to occlusion. There is a sufficient number of examples recorded after some serious thoracic injury to justify the conclusion that trauma may lead to occlusion, but there is the likelihood of coincidence, and even a detailed post-mortem examination might not decide the issue. That coronary thrombosis should result from the strain of exceptional effort seems improbable, although I have seen one patient in whom this possibility could not be dismissed.

There remains for consideration the question of treatment after accident of those patients in whom coronary artery disease may be present. Arenberg (1943) reported an interesting study of 250 men who came under observation for some physical treatment after accident. He made a routine examination of the heart, including an electrocardiogram. It is not easy to assess the significance of the findings because the majority were not seen until several weeks or months after the accident. It was in those patients with hypertension or coronary disease that he found heart disability. The relation of this to trauma cannot be proved, but there is justification for his contention that some might have been saved from symptoms if the heart condition had been considered earlier. Clinical examples of contusion of the heart are not sufficiently common for one observer to gain wide experience. In our own series of patients under observation in this hospital we have gained the impression that older men who had possibly sustained some myocardial bruising did better if they were given a short period of rest than did those who had been getting about in discomfort. Stroud (1940) made a brief editorial comment as follows: 'I still feel cardiac disease is unusual following anterior chest trauma.' For practical clinical purposes this seems to be

a sound dictum. Elderly men, however, may require care and attention after injury, lest their health deteriorate and angina develop. To have been X-rayed with negative result and then dismissed from hospital without advice in relation to some muscular bruising may lead to anxiety about the future. Heberden said of angina 'it is increased by disturbance of the mind'.

Disorders of Rhythm

Auricular fibrillation. Price (1937) and White (1937) stated that auricular fibrillation may develop as the result of trauma or strain. In some accidents there is the element of excitement in addition, and it is not always possible to separate these causes. From the strain of exceptional effort this arrhythmia should come on immediately, but from direct violence there may be delay. The diseased heart is of course much more liable to this event than the healthy. Hay and Jones (1927), however, recorded auricular fibrillation as the result of an exceptional strain in four men, two of them under 40 years of age, in whom they believed the heart to be normal. In one case of my own I should conclude that the heart was normal, although the patient was a man 55 years of age. Acute discomfort develops during or just after the effort. Normal rhythm can be restored by quinidine treatment. In diseased hearts, when fibrillation comes on in the natural course of the complaint, it is possibly due to the result of the frequent small strains of daily life, but it may supervene suddenly on account of some particular effort. Kahn and Kahn (1927) recorded this event in a case of mitral valvular disease, and I have a similar record (Barber, 1938). In another of my patients with hypertensive heart disease who had light work normally, an unexpected emergency effort precipitated this event. Two elderly men knocked down in the street showed auricular fibrillation on admission to hospital, but excitement, strain, and direct violence may all have played some part. Hume (1941) has met with seven examples of auricular fibrillation as a result of strain, but all had valvular disease or hypertension, and the same applies to three cases due to direct violence.

When auricular fibrillation follows direct violence to the thorax, the possibility of a contusion of the heart arises. Kissane (1927) has recorded two such cases, in which a tendency to congestive failure persisted. Warburg (1938) has records of several similar patients some of whom died, as did O'Farrell's (1939) patient. Careful observation and a period of rest are indicated before assessing the heart condition, and considering the question of restoring normal rhythm when the arrhythmia results from direct violence, because there may be a myocardial contusion in addition. Kahn and Kahn (1929) reported a successful case in which normal rhythm was restored by quinidine treatment three months after the accident. Three months later complete recovery was reported. Levison (1927) reported auricular fibrillation lasting 24 hours in a man 20 years of age after a severe crushing injury. There was no other disability. There are some exceptional precipitating causes on record.

Hay and Jones (1927) reported the event after electric shock. Bramwell (1934) described one as the result of head injury, and was cautious in attributing the auricular fibrillation to the injury, but the case seems to be convincing. The man struck his head against a beam, but did not fall or sustain any other injury. I have recently seen a man 44 years of age in whom this arrhythmia was present three months after a severe blow on the head, from which he was unconscious for two hours and was kept in bed at home several days with a scalp wound. Hume (1941) described the case of a woman 58 years of age who developed this arrhythmia after a severe scald of the head, upper chest, and arms. Hamilton (1925) recorded auricular fibrillation which lasted several hours as the result of inhalation of sulphuretted hydrogen, but the full case report (Robinson, 1916) reveals that a healthy man 44 years of age was overcome by the fumes of this gas and fell to the ground, sustaining a scalp wound, so that physical trauma is a possible factor. White and Glendy (1941) have recognized the fumes of this gas as a possible cause, and also inhalation of carbon monoxide. Perhaps these causes are too exceptional to be important, but in relation to carbon monoxide Pulvertaft (1932) described rupture of the heart from acute dilatation in a physically healthy young woman who committed suicide by putting her head in a gas oven. An autopsy 11 hours later revealed a rupture three-quarters of an inch long in the wall of the right ventricle. In summing up the frequency with which auricular fibrillation is related to heart trauma, Warburg (1938, 1940) recorded 51 examples out of 225 cases in which he thought that there was no doubt that the heart sustained injury. In considering the possible structural changes which may dispose toward this disability when it is the result of direct violence, it is important to remember the bruising around the right cardiophrenic angle described by Osborn (1943), which may also lead to tachycardia and sinus bradycardia.

Auricular flutter. This arrhythmia is much less common than fibrillation, but of similar aetiology. There has been one example as the result of trauma in this hospital (Barber, 1938). The condition has been reported by Kahn (1930) in a man 59 years of age from a direct blow over the chest; pain persisted and auricular flutter was recognized three weeks after the accident. There was some congestive failure. He died four months after the injury, but no autopsy was obtained. One would conclude that there had been a contusion of the myocardium. Sigler (1942) described the case of a man 44 years of age who developed calcification of the pericardium as the result of a contusion; on examination three and a half years after the injury auricular flutter was present.

Paroxysmal tachycardia. White and Glendy (1941) stated that auricular paroxysmal tachycardia may be precipitated by injury. We have had two such cases in this hospital, one of which died of pneumonia 10 days after the accident. The other was a man 60 years of age, who fell from a ladder. He bruised his left side but soon recovered. On the third night he became distressed and was sent into hospital. The heart rate was 140 to 150, with

occasional short periods of normal rate. The attacks passed off in about a month.

Nodal tachycardia in a healthy man aged 41 years developed on the third day whilst he was in hospital on account of several fractured ribs on the right side and a haemothorax. His heart rate suddenly rose from 80 to 130–140. The electrocardiogram showed variable findings, in which the P and R waves sometimes coincided, but more frequently the P waves were inverted and followed the R waves. The condition persisted for about 16 days, with the heart rate slowing gradually. There was one short relapse, but a month after the accident the rhythm was normal and the heart rate 80. The circulation was well maintained throughout the attack. He has remained well since and is back at work, although less energetic than before his accident two years ago.

I have one record from the routine electrocardiograms which is of interest in connexion with ectopic beats of the auricle. A man aged 38 years sustained a crushing injury of the thorax and was admitted in a state of shock. There were no injuries of the thoracic wall or other structures. His electrocardiogram two hours after the accident was normal. Two days later he was free from symptoms in bed, except that there was pain behind the sternum if he laughed, but his electrocardiogram showed inversion of the P waves in all four leads. Two days later the electrocardiogram was normal. It is tempting to make a diagnosis of bruising on the posterior aspect of the right auricle, as described by Osborn (1943). Kissane (1937) reported the case of a man 42 years of age who fell on to a step and fractured two ribs; three days later there was severe dyspnoea, and an electrocardiogram showed nodal tachycardia. He died shortly after, the autopsy revealing haemorrhage into the mediastinum and myocardium.

Ventricular tachycardia is more serious, for which condition White and Glendy (1941) recommend quinidine. They refer to Schlomka's (1934) work on induced trauma, but there does not seem to be published clinical evidence.

Sinus bradycardia has been reported in animal experiments. We have met with four examples as the result of direct violence to the thorax. Three were detected in the routine electrocardiograph series, and the fourth did not come to hospital until five days after receiving a severe blow over the chest from a cricket ball. He was a somewhat hysterical youth, and seems to have collapsed at work on account of persistent pain. The heart rate was 44, but rose to 80 a few days later. Of the other three patients, two were free from symptoms and the third (Barber, 1942) felt faint one and a quarter hours after a steering-wheel accident, but had recovered when he came to hospital soon after, where the heart rate was 36. It was 72 a few days later. Kissane (1937) recorded sinus bradycardia in a man 58 years of age who developed dyspnoea two weeks after an accident. There were no other abnormalities except a low blood-pressure which we also noted in our patients. Jokl (1941), analysing the injuries met with in boxing, quoted Külbs (1937) who reported a boy 16 years of age, who a few hours after a fight complained of pain in

the region of the heart. His pulse-rate was 68 to 72. Next day the rate was 32, but there were no other abnormalities in the electrocardiogram or otherwise. The rate quickened with exercise, but persisted as a resting pulse-rate of 32 for 10 weeks, during six of which he was kept in bed. With a slow heart rate after trauma, there is the obvious indication to exclude heart-block, and the more remote one to realize that a patient in a surgical ward with multiple injuries may have a slow pulse of cardiac origin, although a more common cause is cerebral compression.

Heart-block with a fatal termination has been noted in some seriously damaged hearts, There is, however, a number of records of heart-block as the only obvious disability after injury. The most convincing are those in which the condition is temporary, about one-third of the cases, but there are well-authenticated examples of the disability persisting. Warburg (1940) cited 10 examples from medical literature and White and Glendy (1941) two others. Arenberg (1943) recorded heart-block persisting 20 months after direct violence to the chest in a man aged 42 years. Tuohy and Boman (1931) have recorded traumatic heart-block which changed to bundle branch block and finally persisted as complete block. Campbell (1943) mentioned a case of latent heart-block due to blast. In one of the routine electrocardiograms in this hospital there was an example of partial heart-block (Barber, 1942) in a youth who was crushed against a wall by the radiator of a lorry. The abnormal tracing persisted for more than a year; he then left this district. Heart-block of traumatic origin does not appear to be common. The injuries have been somewhat similar to those which have led to delayed rupture of the heart, and essentially it is a form of myocardial contusion. The functional capacity of the heart in those cases where the disability has persisted seems to be reasonably good. Goldman (1941) recorded this condition 14 years after a bullet wound, and commented on the contrast with heart-block due to natural causes in which there is myocardial disease. Tuohy and Boman (1931) recorded temporary partial heart-block after the strain of a heavy lifting effort. The pulse-rate next day was 26 and there was considerable distress. The patient recovered in a month. It is not easy to explain the occurrence of this disorder as the result of strain. I have seen no similar record.

Extrasystolic arrhythmia. The significance of premature contractions is not well enough defined to make it a profitable study in relation to trauma. An electrocardiogram showing two or three in succession, or extrasystoles alternating in direction, might be important. Arenberg (1943) reported the case of a man aged 31 years who fell from a height of 10 feet and struck his chest on a stone floor; he complained of 'palpitation and fluttering' after the accident, but remained at work. Examined six weeks after the accident, there were no abnormalities except numerous extrasystoles, and the symptoms cleared up in about three months without his leaving work. Leinoff (1940) in a healthy man 21 years of age reported numerous nodal extrasystoles after a crushing injury. There was substernal discomfort and shortness of breath.

Ventricular fibrillation. With the animals already connected with the electrocardiograph, Bright and Beck (1935) recorded death from this disorder in two dogs, and Kissane, Fidler, and Koons (1940) noted one such event after induced trauma. If immediate death results from a direct blow over the heart, and there is no evidence *post mortem* to account for the fatality, ventricular fibrillation is a reasonable explanation. Jokl (1941) cited a boxing fatality in which this event seemed probable.

Valvular Lesions

Most valvular lesions the result of trauma have a well-defined history of immediate distress and probably show some unusual physical signs. Unless an autopsy is performed, it may not be possible to determine whether the valve was healthy or already diseased. As an illustration of the prevalence of latent valvular disease of which the patient has no knowledge, Hume (1941) found this in 14 of a group of 64 men who were complaining of symptoms referable to the cardiovascular system after chest injury.

From indirect violence. Rupture of a valve from strain of some exceptional effort has been recognized for at least 150 years. Several examples were recorded by Corvisart early in the nineteenth century. Peacock (1865*a*), in the Croonian Lectures, and Barié (1881) recorded examples. Allbutt (1909) could write—'the cases on record are so many as to make it unnecessary to accumulate examples'. The aortic valves are the most liable to this accident. There is immediate distress, a bruit of unusual intensity, of which the patient may be conscious, and heart failure will supervene. This is usually progressive failure, with a fatal termination before long. In the majority of cases there is reason to believe that the valves were already diseased, although of this the patient may have had no knowledge. But there are records (Howard, 1928; Kissane, Koons, and Fidler, 1936) which seem to prove that a healthy valve may rupture from strain. In either event the results are serious. In the mitral area a traumatic valvular lesion as the result of strain is most likely to be a rupture of the chordae tendinae. Horton-Smith (1902) described this accident in a healthy workman 33 years of age. There was immediate pain with dyspnoea, and the patient died of congestive heart failure in three months' time. At the autopsy there was no evidence of previous disease. Frothingham and Hass (1934) described ruptured chordae tendinae in a man 64 years of age after a strenuous day of exertion, which included rowing and swimming. It is an unusual history, because the ill effects came on when he woke at 2.0 a.m. with urgent dyspnoea and some pulmonary oedema. It is possible that this was an attack of cardiac asthma in which the rupture took place. Congestive failure developed and he died seven months later. Four chordae tendinae of the posterior cusp of the mitral valve were ruptured, but there was no evidence of disease. Kissane and Koons (1938) made this diagnosis in a man 37 years of age who had been passed for life insurance a year before the accident. The illness was the result of cranking a car for about 30 minutes, when immediate pain, dyspnoea,

and dizziness came on. His condition slowly deteriorated, but he was alive eight years later. In all these cases there was a mitral systolic bruit of unusual pitch and intensity. Diseased valves, aortic or mitral, are more liable to rupture, and may do so from a strain of only moderate intensity. Peacock (1865*b*) recorded rupture of chordae tendinae during vomiting in a child with mitral stenosis. Lesions of other valves from similar causes must be very exceptional. Gordon (1922) described the case of a young woman who could hear a noise in her chest after the exertion of running. I have been told by a medical colleague of a similar event. Neither of these patients was much distressed, although in both a loud systolic bruit persisted. A rupture of some defect in the septum or the foramen ovale is a possible explanation. There are one or two records of valve rupture in bacterial endocarditis (Kennedy and McDougall, 1915). The condition has little clinical significance and it is improbable that any medico-legal question could arise.

From direct violence. Kahn and Kahn (1929) and several pathologists of a former generation have recorded that it is possible in the post-mortem room to rupture a valve by direct violence. In experimental work on dogs Bright and Beck (1935) and Kissane, Fidler, and Koons (1940) have recorded valve rupture. There is a sufficient number of case records, however, to make the clinical evidence convincing. Wilks (1865) described the event of a young man who fell from a height, striking his left side on a stone. 'He suffered from dyspnoea, but a stethoscope was not used.' He died in a surgical ward two days later from abdominal injuries, and Wilks recorded that the only cardiac lesion was rupture of the posterior cusp of the aortic valve, which was split from the free edge to the base. There was no sign of chronic disease, but a small deposit of fibrin was found on the torn edges of the valves. Gibson (1909) recorded rupture of the mitral valve from the kick of a horse, immediately fatal. Kissane, Koons, and Fidler (1936) reported rupture of the aortic valves in a man who was buried by an explosion. He died a year later, when the lesion was confirmed. I suppose that in this case internal stress may have played some part. Kemp (1923) described traumatic rupture of the aorta in a man 46 years of age who was struck over the front of the chest by a portion of a stone fly-wheel. There was a haemopericardium due to a transverse tear just above the aortic valves. Mitral valve injuries from direct violence have also been discussed in the present article as a complication of myocardial contusion. Two additional examples are included in the next section, in relation to chronic valvular disease.

Chronic valvular disease. Most traumatic valvular lesions show a well-defined downward course from the injury to their fatal termination. White and Glendy (1941) stated that 'stenosis has never yet been shown to be of traumatic origin'. This statement requires some qualification. A patient of mine (Barber and Osborn, 1937) who sustained a mitral valve lesion from a contusion of the heart could be demonstrated 10 years after the accident

as a typical case of mitral stenosis with presystolic thrill and bruit. At this stage he could get about quietly. After his injury, which was the result of being buried by a shell explosion, he was in bed in hospital or at home for about five years with a mitral systolic bruit as the chief sign of a disorganized mitral valve. There is no doubt that this healed up to mitral stenosis and the trauma was confirmed 22 years after the accident, when he died of pneumonia. There was scar tissue through the left ventricular wall, continuous into the valve. Warburg (1938) recorded a crushing injury of the chest in a man 20 years of age. There was obvious evidence of valvular lesion, but a presystolic mitral bruit was not recognized until three years after the injury. At this time he had improved to a degree where he could undertake light work. These two are quite exceptional cases; by the time mitral stenosis could be diagnosed they had improved in capacity for exertion, and in the absence of a full history and medical evidence the condition would have been mistaken for disease due to natural causes. Allbutt (1873) described mitral stenosis in two young men, in one due to the kick of a horse and in the other to a blow from a cricket ball. He saw both these patients about a year after the accidents and attributed the stenosis to trauma. He did not, however, give details of the life history between the accident and his examination, although the symptoms just after the accidents are described as alarming. We have not the proof which White and Glendy (1941) rightly require. From the animal experiments we know that trauma may sometimes cause bruising, chiefly at the base of the valves, and it is possible that this might lead to some degree of fusion of the cusps. I have seen one post-mortem specimen of stenosis of the aortic valves in a man who died of bronchitis. There was a fracture of the sternum over the base of the heart, which had been due to a fall of roof whilst he was in bed 20 years previously. The aorta, coronary arteries, mitral valve, and heart muscle were healthy. The condition was suggestive of trauma, but in the absence of a detailed medical history no conclusions can be drawn. The patients with aortic regurgitation after injury have in nearly all cases shown immediate evidence of serious valvular lesion. Sigler (1942), however, examined a man of 39 years of age five months after a crushing injury of the chest. The chief complaint was angina of effort. Sigler could detect some degree of aortic regurgitation, but the signs were much more pronounced a year subsequently. The radiological evidence suggested that perhaps the aortic ring was dilated.

TABLE II

Summary of clinical cases related to heart trauma, which have been under the writer's own observation. The date follows those cases of which a note has been published. The experience extends from 1908 to 1944, but only in the last eight years have the cases been specifically sought.

From direct violence.

Pericarditis: three cases in the accident ward with pericardial rub; all recovered. One case with myocardial contusion in addition (1942).

Haemopericardium: one case (1940).

Myocardial contusion:

(1) Proved *post mortem*: two cases (1940, 1941).
(2) With characteristic clinical features: three cases (1938, 1940).
(3) With clinical symptoms and electrocardiographic proof: two cases (one, 1942).
(4) Evidence from 75 routine electrocardiograms (Table I) suggested 11 examples of myocardial or pericardial bruising. Most of these patients were distressed on account of associated injuries, but two with temporary abnormality in Leads I and IV showed clinical evidence of heart disability which passed off in one or two weeks.
(5) Angina of effort after thoracic trauma: four cases (two, 1938).
(6) Persistent functional incapacity after chest injury: five cases (two, 1938).
(7) Heart-block: one partial heart-block after crushing injury (1942).

Valvular lesions: one example from direct violence of disorganized mitral valve, which healed up to stenosis; trauma confirmed at autopsy 22 years later (1937).

From strain of exceptional effort.

Rupture of aortic valve cusp: one case, valve probably diseased. Coronary thrombosis: one case, with history apparently convincing. Primary cardiac overstrain: two cases (one, 1938).

Disorders of rhythm related to trauma.

Auricular fibrillation:

(1) From direct violence of being knocked down by a car: two cases (1938).
(2) After a head injury: one case.
(3) From exceptional strain of healthy heart: one case, a patient aged 55 years.
(4) From strain of diseased heart: three cases (one, 1938).

Auricular flutter: one case in patient with fracture of cervical spine (1938).
Supraventricular tachycardia: three cases from direct violence.
Sinus bradycardia: four cases as the result of blow over chest (one, 1942).
Extrasystolic arrhythmia: two cases with symptoms; one from direct violence (1938) and one in primary cardiac overstrain.

Summary

1. Traumatic heart lesions the result of penetrating wounds, direct violence, and exceptional strain are reviewed.

2. Penetrating wounds are discussed only briefly. The practical experience gained in the present war has not yet been recorded fully.

3. The evidence from the morbid anatomy and from the experimental work on animals suggests that bruising of the myocardium is fairly common as the result of non-penetrating injuries or contusion of the heart. There are records of well-defined clinical cases, but the evidence does not indicate that serious heart disability, either temporary or permanent, is a common sequel of thoracic trauma.

4. The diseased heart is more prone to suffer as the result of exceptional strain than is the healthy, but when the coronary arteries are diseased, it is difficult to assess the significance of an injury.

5. Disorders of rhythm the result of direct violence or exceptional strain simulate disease due to natural causes.

6. Most of the evidence with regard to traumatic valvular lesions was well established a generation ago.

7. It is suggested that an exceptional effort, with the chest fixed and the glottis closed, may on rare occasions give rise to primary cardiac overstrain of a heart previously healthy.

8. There is included a synopsis of routine electrocardiograms in 75 patients shortly after they had sustained a thoracic injury. In 20 there was some abnormality of the tracing. This indicates that in cases of accident such an examination is of importance, but does not justify the conclusion that this proportion of patients is likely to develop heart disability after thoracic trauma.

My thanks are due to my surgical colleagues for giving me facilities to work in the accident wards, and to Dr. G. J. C. Brittain and Mr. G. Lovell Stiles for getting in touch with accident casualties on arrival at hospital.

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and dizziness came on. His condition slowly deteriorated, but he was alive eight years later. In all these cases there was a mitral systolic bruit of unusual pitch and intensity. Diseased valves, aortic or mitral, are more liable to rupture, and may do so from a strain of only moderate intensity. Peacock (1865*b*) recorded rupture of chordae tendinae during vomiting in a child with mitral stenosis. Lesions of other valves from similar causes must be very exceptional. Gordon (1922) described the case of a young woman who could hear a noise in her chest after the exertion of running. I have been told by a medical colleague of a similar event. Neither of these patients was much distressed, although in both a loud systolic bruit persisted. A rupture of some defect in the septum or the foramen ovale is a possible explanation. There are one or two records of valve rupture in bacterial endocarditis (Kennedy and McDougall, 1915). The condition has little clinical significance and it is improbable that any medico-legal question could arise.

From direct violence. Kahn and Kahn (1929) and several pathologists of a former generation have recorded that it is possible in the post-mortem room to rupture a valve by direct violence. In experimental work on dogs Bright and Beck (1935) and Kissane, Fidler, and Koons (1940) have recorded valve rupture. There is a sufficient number of case records, however, to make the clinical evidence convincing. Wilks (1865) described the event of a young man who fell from a height, striking his left side on a stone. 'He suffered from dyspnoea, but a stethoscope was not used.' He died in a surgical ward two days later from abdominal injuries, and Wilks recorded that the only cardiac lesion was rupture of the posterior cusp of the aortic valve, which was split from the free edge to the base. There was no sign of chronic disease, but a small deposit of fibrin was found on the torn edges of the valves. Gibson (1909) recorded rupture of the mitral valve from the kick of a horse, immediately fatal. Kissane, Koons, and Fidler (1936) reported rupture of the aortic valves in a man who was buried by an explosion. He died a year later, when the lesion was confirmed. I suppose that in this case internal stress may have played some part. Kemp (1923) described traumatic rupture of the aorta in a man 46 years of age who was struck over the front of the chest by a portion of a stone fly-wheel. There was a haemopericardium due to a transverse tear just above the aortic valves. Mitral valve injuries from direct violence have also been discussed in the present article as a complication of myocardial contusion. Two additional examples are included in the next section, in relation to chronic valvular disease.

Chronic valvular disease. Most traumatic valvular lesions show a well-defined downward course from the injury to their fatal termination. White and Glendy (1941) stated that 'stenosis has never yet been shown to be of traumatic origin'. This statement requires some qualification. A patient of mine (Barber and Osborn, 1937) who sustained a mitral valve lesion from a contusion of the heart could be demonstrated 10 years after the accident

as a typical case of mitral stenosis with presystolic thrill and bruit. At this stage he could get about quietly. After his injury, which was the result of being buried by a shell explosion, he was in bed in hospital or at home for about five years with a mitral systolic bruit as the chief sign of a disorganized mitral valve. There is no doubt that this healed up to mitral stenosis and the trauma was confirmed 22 years after the accident, when he died of pneumonia. There was scar tissue through the left ventricular wall, continuous into the valve. Warburg (1938) recorded a crushing injury of the chest in a man 20 years of age. There was obvious evidence of valvular lesion, but a presystolic mitral bruit was not recognized until three years after the injury. At this time he had improved to a degree where he could undertake light work. These two are quite exceptional cases; by the time mitral stenosis could be diagnosed they had improved in capacity for exertion, and in the absence of a full history and medical evidence the condition would have been mistaken for disease due to natural causes. Allbutt (1873) described mitral stenosis in two young men, in one due to the kick of a horse and in the other to a blow from a cricket ball. He saw both these patients about a year after the accidents and attributed the stenosis to trauma. He did not, however, give details of the life history between the accident and his examination, although the symptoms just after the accidents are described as alarming. We have not the proof which White and Glendy (1941) rightly require. From the animal experiments we know that trauma may sometimes cause bruising, chiefly at the base of the valves, and it is possible that this might lead to some degree of fusion of the cusps. I have seen one post-mortem specimen of stenosis of the aortic valves in a man who died of bronchitis. There was a fracture of the sternum over the base of the heart, which had been due to a fall of roof whilst he was in bed 20 years previously. The aorta, coronary arteries, mitral valve, and heart muscle were healthy. The condition was suggestive of trauma, but in the absence of a detailed medical history no conclusions can be drawn. The patients with aortic regurgitation after injury have in nearly all cases shown immediate evidence of serious valvular lesion. Sigler (1942), however, examined a man of 39 years of age five months after a crushing injury of the chest. The chief complaint was angina of effort. Sigler could detect some degree of aortic regurgitation, but the signs were much more pronounced a year subsequently. The radiological evidence suggested that perhaps the aortic ring was dilated.

TABLE II

Summary of clinical cases related to heart trauma, which have been under the writer's own observation. The date follows those cases of which a note has been published. The experience extends from 1908 to 1944, but only in the last eight years have the cases been specifically sought.

From direct violence.

Pericarditis: three cases in the accident ward with pericardial rub; all recovered. One case with myocardial contusion in addition (1942).

Haemopericardium: one case (1940).

Myocardial contusion:

(1) Proved *post mortem*: two cases (1940, 1941).
(2) With characteristic clinical features: three cases (1938, 1940).
(3) With clinical symptoms and electrocardiographic proof: two cases (one, 1942).
(4) Evidence from 75 routine electrocardiograms (Table I) suggested 11 examples of myocardial or pericardial bruising. Most of these patients were distressed on account of associated injuries, but two with temporary abnormality in Leads I and IV showed clinical evidence of heart disability which passed off in one or two weeks.
(5) Angina of effort after thoracic trauma: four cases (two, 1938).
(6) Persistent functional incapacity after chest injury: five cases (two, 1938).
(7) Heart-block: one partial heart-block after crushing injury (1942).

Valvular lesions: one example from direct violence of disorganized mitral valve, which healed up to stenosis; trauma confirmed at autopsy 22 years later (1937).

From strain of exceptional effort.

Rupture of aortic valve cusp: one case, valve probably diseased. Coronary thrombosis: one case, with history apparently convincing. Primary cardiac overstrain: two cases (one, 1938).

Disorders of rhythm related to trauma.

Auricular fibrillation:

(1) From direct violence of being knocked down by a car: two cases (1938).
(2) After a head injury: one case.
(3) From exceptional strain of healthy heart: one case, a patient aged 55 years.
(4) From strain of diseased heart: three cases (one, 1938).

Auricular flutter: one case in patient with fracture of cervical spine (1938).
Supraventricular tachycardia: three cases from direct violence.
Sinus bradycardia: four cases as the result of blow over chest (one, 1942).
Extrasystolic arrhythmia: two cases with symptoms; one from direct violence (1938) and one in primary cardiac overstrain.

Summary

1. Traumatic heart lesions the result of penetrating wounds, direct violence, and exceptional strain are reviewed.

2. Penetrating wounds are discussed only briefly. The practical experience gained in the present war has not yet been recorded fully.

3. The evidence from the morbid anatomy and from the experimental work on animals suggests that bruising of the myocardium is fairly common as the result of non-penetrating injuries or contusion of the heart. There are records of well-defined clinical cases, but the evidence does not indicate that serious heart disability, either temporary or permanent, is a common sequel of thoracic trauma.

4. The diseased heart is more prone to suffer as the result of exceptional strain than is the healthy, but when the coronary arteries are diseased, it is difficult to assess the significance of an injury.

5. Disorders of rhythm the result of direct violence or exceptional strain simulate disease due to natural causes.

6. Most of the evidence with regard to traumatic valvular lesions was well established a generation ago.

7. It is suggested that an exceptional effort, with the chest fixed and the glottis closed, may on rare occasions give rise to primary cardiac overstrain of a heart previously healthy.

8. There is included a synopsis of routine electrocardiograms in 75 patients shortly after they had sustained a thoracic injury. In 20 there was some abnormality of the tracing. This indicates that in cases of accident such an examination is of importance, but does not justify the conclusion that this proportion of patients is likely to develop heart disability after thoracic trauma.

My thanks are due to my surgical colleagues for giving me facilities to work in the accident wards, and to Dr. G. J. C. Brittain and Mr. G. Lovell Stiles for getting in touch with accident casualties on arrival at hospital.

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Wing-Com. Kenneth Robson, M.D.
Assistant Physician, St. George's Hospital.

Alfred Brian Taylor, M.D.
Assistant Physician, Birmingham United Hospital.

Lt.-Col. Ronald Ernest Tunbridge, M.D.
Honorary Physician, Leeds Public Dispensary.

Lt.-Col. Arthur Willcox, M.D.
Medical Registrar, Middlesex Hospital.

INDEX